Breakthrough in the treatment of nausea and vomiting of pregnancy; the first dual release combination of doxylamine-pyridoxine

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Abstract

Nausea and vomiting of pregnancy (NVP) affect up to 85 % of all pregnancies. Effective treatment can improve woman's quality of life, reduce the risk for maternal and fetal complications, and reduce healthcare costs. Because women tend to date to postpone the start of their family into their thirties, increasing numbers of them suffer from chronic conditions necessitating internal medicine specialists, and hence NVP is increasingly a clinical issue the internist needs to deal with. The only agent approved by the FDA and other countries for the management of NVP symptoms and recommended by leading healthcare and professional organizations, has been the delayed release combination of doxylamine and pyridoxine. This combination, formulated as a 10 mg/10 mg delayed release tablet, was approved by the US Food and Drug Administration (FDA) for the treatment of NVP in April 2013 (Diclegis®).

Due to its delayed release properties, it begins to exert its antiemetic properties 6-8 hours after ingestion, and hence symptom relief may be delayed and necessitate the use of an immediate release medication. In November 2016 the FDA approved Bonjesta®, a novel, dual- release combination of doxylamine and pyridoxine, whereby a rapid release phase is followed by a delayed release phase, thus overcoming the time delay in action of the delayed release combination of doxylamine and pyridoxine . In this article we review the unique properties of this new drug which is only the second FDA- approved agent for the treatment of NVP.

Keywords: nausea and vomiting of pregnancy, doxylamine, pyridoxine, pyridoxal 5 phosphate, dual release doxylamine-pyridoxine combination, Pregnancy- unique quantification of emesis (PUQE), delayed release combination of doxylamine-pyridoxine combination

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1. Introduction

1.1 The Etiology of NVP

The etiology of NVP remains unknown, contributing to the difficulty in management of the condition [1–4]. The most common theory is that hormonal increase during the first trimester of pregnancy, specifically the human chorionic gonadotropin (hCG), estrogen and progesterone, contribute to NVP. Repeated studies and a meta-analysis have shown an association between Helicobacter pylori infection and severe NVP [5-7]. Genetic susceptibility for NVP include familial recurrence, monozygotic twin pair correlation, and previous history of HG [2,8,9].

1.2 Clinical Aspects of NVP

1.2.1. Time and severity

NVP affects up to 85 % of pregnant women. The term ‘‘morning sickness’’ commonly used for this condition is inappropriate as the symptoms of NVP can occur throughout the day and/or night [1]. Symptoms of NVP include nausea, gagging, retching and/or vomiting typically commencing between 4 and 9 weeks of pregnancy, peaking between 7 and 12 weeks, and in the majority of women subside by 12 to 16 weeks of pregnancy; however, in up to 15 %of women, symptoms continue till 20 weeks of gestation, and up to 10 % of women suffer throughout their entire pregnancy [2, 3].

The severity of NVP can range from mild to severe and it is best quantified by combining the degree of nausea, vomiting and retching (Table 1). The most severe form of NVP, hyperemesis gravidarum (HG), affects between 0.3–2 % of pregnancies and commonly requires hospitalization because of severe and persistent nausea and vomiting, weight loss of greater than 5 %, dehydration, electrolyte imbalances, and nutritional deficiencies [2–4].

Women who have had NVP in a previous pregnancy are more likely to have recurrence of NVP in subsequent pregnancies. Repeated studies demonstrated that initiating antiemetic treatment prior to the first day of symptoms effectively lessen the severity of symptoms and reduce the recurrence of HG in women who experienced severe NVP in a previous pregnancy [10-11].

1.2.2. Quality of life

NVP can adversely impact women’s quality of life and well-being [3, 12, 13] characterized by frustration, helplessness, resentfulness, and depression [14,15]. These feelings negatively affect women’s social and family life, with approximately half of women reporting adverse effects on their marital relationships [15]. In severe cases of NVP, some women choose to electively terminate their pregnancy; In a study of 3,201 pregnant women experiencing NVP, 108 reported to have terminated their pregnancy due to NVP, and an additional 413 considered termination [16].

1.2.3 Economic burden

NVP bears a significant financial burden on women, their families and society [17,18]. The 2012 total economic burden of NVP in the USA was estimated at US$ 1,778,473,782-—60 % in direct costs and 40 % in indirect costs, with the average cost of US$ 1,827 to manage each case [18].

1.3 Management of NVP

Women with mild NVP often find lifestyle and dietary modifications to sufficiently manage their symptoms [19]. Additionally, non-pharmacological interventions such as acupressure bands, acupuncture or ginger root powder capsules are often used; however their reported effectiveness has been inconsistent [19, 20].

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While a relatively large number of antiemetic drugs have been proven effective in the treatment of nausea and vomiting caused by chemotherapy, motion sickness, GI conditions or cyclic vomiting [21], their use in pregnancy is marred by lack of sufficient data on effectiveness and fetal safety [22]. The only drug approved and indicated for the treatment of NVP in the USA, Canada and some other countries is the delayed-release formulation of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride (HCl), after being proven both effective and safe [23-27]. This combination is currently available in the USA and leading professional organizations, such as the American College of Obstetrics and Gynecology (ACOG) [28], the American Professors of Gynecology and Obstetrics [3], and the Society of Obstetricians and Gynecologists of Canada [29], as well as teratogen information services, such as Mother to Baby [30], recommend the delayed release combination of doxylamine and pyridoxine as first-line therapy for the treatment of NVP. This recommendation is based on the extensive fetal safety and maternal efficacy data available for this medication.

Due to its pharmacokinetic properties, the delayed release combination of doxylamine and pyridoxine begins to exert its antiemetic properties 6-8 hours after ingestion, and hence symptom relief may be delayed and necessitate the use of an immediate release medication. In November 2016 the FDA approved Bonjesta®, a novel, dual- release combination of doxylamine and pyridoxine, whereby a rapid release phase is followed by the delayed release phase, thus overcoming the time delay in action of the delayed release combination of doxylamine and pyridoxine.

The objective of this review is to introduce a novel dual release combination of doxylamine and pyridoxine. We will first discuss the effectiveness and fetal safety of the two doxylamine and pyridoxine, followed by detailed description of the drug itself.

2. History of Doxylamine/Pyridoxine

This combination was first introduced in the USA as Bendectin® in 1956. Initially, it was formulated as a delayed-release combination of 10 mg doxylamine succinate, 10 mg pyridoxine, and 10 mg dicyclomine HCl [23, 31]. However, in 1976, an eight-way study of doxylamine, pyridoxine HCl, and dicyclomine showed that dicyclomine did not confer an independent antiemetic effect, and consequently, Bendectin® was reformulated to contain only 10 mg doxylamine succinate and 10 mg pyridoxine HCl [32-34]. Importantly, no other doxylamine-containing product has a Pregnancy Category A rating, the safest, by the FDA. While the parent drug doxylamine has been shown to be antiemetic, a 2014 study suggests that for pyridoxine it is the pyridoxal 5 phosphate metabolite which is the bioactive [35].

The dose of the delayed-release doxylamine/pyridoxine for NVP is typically up to four tablets daily: two tablets at bedtime, one in the morning, and one in the mid-afternoon. This delayed-release formulation permits the antiemetic action to occur 4–6 h after ingestion; therefore, the bedtime dose would be effective in the early morning, the morning dose would be effective in the afternoon and the mid-afternoon dose would be effective in the evening, providing 24 h control of NVP symptoms. It does have the shortcoming of lack of immediate effect, which was one of the reasons for the development of the dual release combination of doxylamine and pyridoxine.

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3. Clinical Effectiveness of the Delayed-Release Combination of Doxylamine/ Pyridoxine

The clinical effectiveness of the delayed-release combination of doxylamine and pyridoxine has been documented in a large number of randomized, controlled trials and open, controlled post-marketing studies[36-39].

Strong evidence supporting the effectiveness of this delayed-release combination was provided by population-based studies conducted in the USA and Canada showing that its withdrawal from the American and Canadian markets was temporally related to a two- to threefold increase in the rates of hospitalization of women for NVP [33,40]. These data suggest that the doxylamine/pyridoxine combination is not only capable of eradicating mild and moderate forms of NVP, but also of preventing severe cases. Data from Neutel [40] reiterate these findings: the increased use of the delayed release combination of doxylamine and pyridoxine by Canadian women during the 1990s has been associated with a reduction in the hospitalization rate of women for severe NVP.

4. The Dual Release Combination of Doxylamine-Pyridoxine

The dual release combination of doxylamine and pyridoxine .was approved by the FDA in November 2016 for the treatment of NVP when conservative management fails and it has been introduced to the American market in April 2018.[41]. This labeling is based on the results of controlled studies that have not shown increased risk of adverse effects to an unborn baby and on the numerous efficacystudied

The drive for the development of a novel, optimized reformulation of the delayed release combination of doxylamine and pyridoxine .stemmed from several objectives:

1) To combine a fast acting form of doxylamine/pyridoxine with the delayed release form, thus conferring an immediate antiemetic effect which was not available with the delayed release combination.

2) To decrease dosing from three times/day (morning, noon and evening) to twice a day, thus aiming to improve women's adherence during the challenging days of nausea and vomiting symptomatology.
3) To decrease variability in serum concentrations of the active components of the medication. The delayed release combination allows sufficient levels of doxylamine and the active metabolite pyridoxal 5 phosphate in the systemic circulation at waking time (approximately 8 am) to provide morning NVP relief. However, the morning dose may not provide sufficiently rapid therapeutic levels, which the new dual release combination provides.

4.1. Formulation and dose:

The dual release combination of doxylamine and pyridoxine, a faster acting, longer lasting optimized reformulation of the delayed release agent, is a multilayer, extended-release tablet consisting of an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and an immediate-release coating of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, delivering a total of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride (Figure 1).

The dual feature of the new formulation allows for a rapid relief of NVP symptoms, and for sustained therapeutic

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effect, controlling nausea and vomiting symptoms that occur in the morning, throughout the day and into the night. The immediate-release portion in the coating layer allows for a fast rate of absorption and a rapid relief of NVP symptoms. Importantly, the absorption of the immediate-release portion of the dual release combination is not affected by food. The immediate-release coating along with the delayed-release enteric-coated core make it an extended-release drug with a continuous pharmacodynamic effect.

The dose of each active ingredient in the dual release combination of doxylamine and pyridoxine .tablets is double that of the delay release formulation, so the maximum daily recommended dosing is decreased from four tablets with the delayed release to two tablets per day with the dual release (i.e. one tablet in the morning and one tablet at bedtime), resulting in the same maximum daily dose as the delayed release formulation. Therefore, the formulation and schedule of administration of the dual release formula reduces the pill burden and is likely to improve patient adherence. This is based on a secondary analysis of a double-blind randomized controlled trial conducted with the delayed-release combination of doxylamine succinate and pyridoxine hydrochloride (the same ingredients found in the dual release), which demonstrated that the average number of tablets per day was negatively associated with adherence[42]. This is clinically important especially for pregnant women suffering from nausea and vomiting and have difficulties in swallowing tablets and need to take frequent small meals. In addition, by reducing the pill burden, improved patient adherence may reduce variations in the effective concentrations of doxylamine and pyridoxal 5'-phosphate plasma, ensuring that the dual release combination.provides a sustained therapeutic effect.

The dual release formulation should be taken as a daily prescription, and not on an as-needed basis, in order to achieve therapeutic steady-state concentrations of the active ingredients for optimal anti-nauseant and anti-emetic effects. After administration of the dual release formulation due to its immediate-release portion, there is a rapid onset of action followed by the delayed action. The dosing regimen begins with one tablet taken at bedtime (Day 1). If NVP symptoms persist on Day 2, a second tablet is to be added in the morning to control NVP symptoms throughout the day. Hence, the maximum recommended dose is two tablets per day, one in the morning and one at bedtime.

4.2 The Pharmacokinetic Novelty of the Dual Release Combination of Doxylamine and Pyridoxine .

For the purpose of development of the dual release formulation, its pharmacokinetics was studied exclusively in healthy adult females to ensure that they relate directly to women of reproductive age.

In a single-dose, crossover study conducted in 48 healthy, premenopausal women under fasting conditions, one dual release tablet (20 mg doxylamine succinate and 20 mg pyridoxine) was bioequivalent to two combination tablets of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride based on systemic exposure (measured as the area under concentration time curve-AUC) and peak concentrations (Cmax) of doxylamine and baseline corrected pyridoxal 5′-phosphate, the active metabolite of pyridoxine. Mean ± SD plasma (whole blood for pyridoxal) pharmacokinetic parameters are summarized in Table 2.

In a multiple-dose, crossover clinical trial, one dual release (20 mg doxylamine succinate and 20 mg pyridoxine) tablet given twice daily for 11 days was

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bioequivalent to one combination tablet of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride given three times daily (1 tablet in the morning, 1 tablet in the afternoon and 2 tablets at bedtime) (Table 3).

In a single-dose, crossover clinical trial, the administration of a high fat, high calorie meal delayed the absorption of doxylamine, pyridoxine, and pyridoxine metabolites. This delay was associated with lower peak concentrations of doxylamine, pyridoxine, and pyridoxal. The extent of absorption for pyridoxine was decreased (Table 4).

The effect of food on the peak concentration and the extent of absorption of the pyridoxine component is more complex because pyridoxine metabolites such as pyridoxal, pyridoxamine, pyridoxal 5′-phosphate, and pyridoxamine 5′-phosphate also contribute to the biological antiemetic activity. Food significantly reduces the bioavailability of pyridoxine, lowering its Cmax and AUC by approximately 67% and 37%, respectively, compared to fasting conditions. Similarly, food significantly reduces pyridoxal Cmax by approximately 46% compared to fasting conditions. In contrast, food did not affect pyridoxal 5′-phosphate Cmax and AUC. The unique characteristics of the dual release combination of doxylamine and pyridoxine with the early peak concentrations achieved by the immediate release coat, are shown in Figure 3.

Compared to the delayed release agent, the dual release formulation showed a faster onset of action (T_{max}), even when the steady state has been reached. Indeed, median T_{max} on Day 11 for doxylamine was 3.5 hours with dual released combination, compared to 21 hours with the delayed release form. This is due to the immediate-release portion in the coating of the dual release combination that delivers parent drugs rapidly. The dual and delay release formulations had similar AUC and C_{max}, profiles at steady state, therefore the dual release can be considered as safe as the delay release preparation,

5. Clinical Context of the Introduction of the Dual Release Combination of Doxylamine and Pyridoxine.

Because women tend to date to postpone the start of their family into their thirties, increasing numbers of them suffer from chronic conditions necessitating internal medicine specialists, and hence NVP is increasingly a clinical issue the internist needs to deal with. The dual release formulation is only the second FDA-approved medication indicated for the treatment of NVP when conservative management fails. The combination of doxylamine succinate and pyridoxine hydrochloride has been the subject of numerous clinical trials and epidemiological studies presented above.

Although other products, such as promethazine (formerly classified as Pregnancy Category C) metoclopramide ondansetron (formerly classified as Pregnancy Category B), are currently used off-label for the management of NVP, none are specifically indicated for use in pregnancy. In fact, these products were developed for indications other than the treatment of NVP, and their respective prescribing information state that there are no adequate and well-controlled studies in pregnant women [43, 44].

Moreover, although pyridoxine and doxylamine are available OTC in other products and have been used off-label for many years to treat NVP, potential disadvantages of using such generic preparations include the inconvenience of splitting tablets into appropriate doses, purchasing and using multiple products, identifying the correct version of product to

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use, and the lack of extended-release effects that allows for sustained control of NVP symptoms during the morning, and throughout the day and night. In example, only one out of the five versions of the sleep aid Unisom®, with similar-sounding names, contains doxylamine. The four other versions of this OTC brand use different ingredients, such as diphenhydramine, acetaminophen and melatonin, which make them prone to selection error. Evidence of such selection errors abound on numerous blogs and forums. In addition, these OTC products do not have the critical immediate action combined with delayed-release properties, nor are they labeled for use in pregnancy or indicated for the treatment of NVP, which may lead to confusion or concern.

6. Conclusions

The combination of immediate release with a delayed action is unique to the dual release combination of doxylamine and pyridoxine as it allows for the bedtime dose to be effective immediately and also provide with sustained control of NVP symptoms throughout the day. The dual release combination provides a faster onset of action, reduced pill burden, potential improvement in patient adherence, less variation in effective serum concentrations, and shorter delay in absorption if taken with food.

Conflict of Interest declaration:

GK is a consultant for Duchesnay Inc, MV is a employee of Duchesnay Inc.

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References

1. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol. 2000;182(4):931–7.
2. Clark SM, Costantine MM, Hankins GD. Review of NVP and HG
and early pharmacotherapeutic intervention. Obstet Gynecol Int. 2012;252676(10):24.
3. APGO. Nausea and vomiting of pregnancy. APGO Educational series on women's health issues. Boston: Jespersen & Associates, LLC; 2013.
4. Goodwin TM. Hyperemesis gravidarum. Obstet Gynecol Clin North Am. 2008;35(3):401–17.
5. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol. 2007;110(3):695–703.
6. Sandven I, Abdelnoor M, Nesheim BI, Melby KK. Helicobacter pylori infection and hyperemesis gravidarum: a systematic review and meta-analysis of case–control studies. Acta Obstet Gynecol Scand. 2009;88(11):1190–200.
7. Vikanes AV, Stoer NC, Gunnes N, Grjibovski AM, Samuelsen SO, Magnus P, et al. Helicobacter pylori infection and severe hyperemesis gravidarum among immigrant women in Norway: a case–control study. Eur J Obstet Gynecol Reprod Biol. 2013;167(1):41–6.
8. Fejzo MS, Macgibbon KW, Romero R, Goodwin TM, Mullin PM. Recurrence risk of hyperemesis gravidarum. J Midwifery Womens Health. 2011;56(2):132–6. 9. Fejzo MS, Ingles SA, Wilson M, Wang W, MacGibbon K, Romero R, et al. High prevalence of severe nausea and vomiting ofmpregnancy and hyperemesis gravidarum among relatives of
affected individuals. Eur J Obstet Gynecol Reprod Biol.2008;141(1):13–7.
10. Koren G, Maltepe C. Pre-emptive therapy for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. J Obstet Gynaecol. 2004;24(5):530–3.
11. Maltepe C[1], Koren G. Preemptive treatment of nausea and vomiting of pregnancy: results of a randomized controlled trial. Obstet Gynecol Int. 2013;2013:809787. doi: 10.1155/2013/809787. Epub 2013 Feb 17.
12. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol.
2002;186(5 Suppl Understanding):S220–7.
13. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? Bjog. 2008;115(12):1484–93.
14. Nguyen P, Einarson A. Managing nausea and vomiting of pregnancy with pharmacological and nonpharmacological treatments. Women's health (London, England). 2006;2(5):753–60.
15. Miller F. Nausea and vomiting in pregnancy: the problem of perception—is it really a disease? Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S182–3.
16. Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy.
J Psychosom Obstet Gynaecol. 2001;22(1):7–12.
17. Piwko C, Ungar WJ, Einarson TR, Wolpin J, Koren G. The weekly cost of nausea and vomiting of pregnancy for women calling the Toronto Motherisk Program. Curr Med Res Opin.
2007;23(4):833–40.
18. Piwko C, Koren G, Babashov V, Vicente C, Einarson TR. Economic burden of nausea and vomiting of pregnancy in the USA. J Popul Ther Clin Pharmacol. 2013;20(2):10.

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19. Einarson A, Maltepe C, Boskovic R, Koren G. Treatment of nausea and vomiting in pregnancy: an updated algorithm. Can Fam Physician. 2007;53(12):2109–11.
20. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2003;4: CD000145.
21. Scorza K, Williams A, Phillips JD, Shaw J. Evaluation of nausea and vomiting. Am Fam Physician. 2007;76(1):76–84.
22. Gill SK, Einarson A. The safety of drugs for the treatment of nausea and vomiting of pregnancy. Expert Opin Drug Saf. 2007;6(6):685–94.
23. Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen–litigen. Reprod Toxicol. 1995;9(4):337–49.
24. Einarson TR, Leeder JS, Koren G. A method for meta-analysis of epidemiological studies. Drug Intell Clin Pharm. 1988;22(10): 813–24.
25. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta analysis of the epidemiologic studies. Teratology. 1994;50(1):27–37.
26. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S256–61.
27. Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010;203(6):16.
28. ACOG. ACOG (American College of Obstetrics and Gynecology) practice bulletin: nausea and vomiting of pregnancy. Obstet Gynecol. 2018;131(1):e15-e30.
29. SOGC. Clinical practice guidelines. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2016;38(12):1127-1137.
30. MothertoBaby. Nausea and vomiting. In: Maternal medical conditions fact sheets. http://www.mothertobaby.org/files/Nausea_and_Vomiting_7_13_2.pdf. 2013.
31. http://www.bendectin.com. Accessed: October 01, 2013.
32. Brent R. Bendectin and birth defects: hopefully, the final chapter. Birth Defects Res A Clin Mol Teratol. 2003;67(2):79–87.
33. Kutcher JS, Engle A, Firth J, Lamm SH. Bendectin and birth defects. II: ecological analyses. Birth Defects Res A Clin Mol Teratol. 2003;67(2):88–97.
34. Bendectin Peer Review Report 1975. Overall summary of 8-way Bendectin Study (unpublished study from the FDA databan DESI-10598). FDA1975 Contract No.: DESI 10598.
35. Matok I, Clark S, Caritis S, et al: Studying the antiemetic effect of vitamin B6 for morning sickness; pyridoxine and pyridoxal are prodrugs. J Clin Pharmacol 2015; 54:1429-33
36. Geiger CJ, Fahrenbach DM, Healey FJ. Bendectin in the treatment of nausea and vomiting in pregnancy. Obstet Gynecol. 1959;14:688–90.
37. McGuinness BW, Binns DT. 'Debendox' in pregnancy sickness. J R Coll Gen Pract. 1971;21(109):500–3.
38. Wheatley D. Treatment of pregnancy sickness. Br J Obstet Gynaecol. 1977;84(6):444–7.
39. Bishai R, Mazzotta P, Atanackovic G, Levichek Z, Pole M, Magee LA, et al. Critical appraisal of drug therapy for nausea and vomiting of pregnancy: II. Efficacy and safety of Diclectin (doxylamine-B6). Can J Clin Pharmacol. 2000;7(3):138–43.
40. Neutel CI, Johansen HL. Measuring drug effectiveness by default: the case of

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Bendectin. Can J Public Health. 1995;86(1):66–70.
41. Duchesnay Inc. Bonjesta Full Prescribing Information. Blainville, Quebec, Canada. 2016
42. Costantine MM, Matok I, Chiossi G, et al. Determinants of Adherence to Delayed-Release Doxylamine and Pyridoxine in Patients With Nausea and Vomiting of Pregnancy. Ther Drug Monit 2012;34:569-73.
39. Food and Drug Administration. Center for Drug Evaluation and Research: NDA 209661, Summary Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209661Orig1s000SumR.pdf. November 7, 2016.
43.GlaxoSmithKline. Zofran Full Prescribing Information. Research Triangle Park, NC, United States. October 2016.
44. Sandoz Inc. Promethazine Hydrochloride Full Prescribing Information. Princeton, NJ, United States. April 2014.

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Table 1. A validated method for quantifying the severity of symptoms of nausea and vomiting of pregnancy[27].

Pregnancy-Unique Quantification of Emesis (PUQE): Validated Scoring System for NVP [1,2]

Question	Point Value					Enter
1) In the last 24 hours for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hour (5)	4
2) In the last 24 hours have you vomited or thrown up?	7 or more times (5)	5-6 times (4)	3-4 times (3)	1-2 times (2)	I did not throw up (1)	2
3) In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	7 or more times (5)	
Sum point values for the 3 questions to find the PUQE Score				PUQE Score		

PUQE Score	≤ 6	7-12	13-15
NVP Severity	Mild (3 = no symptoms)	Moderate	Severe

1. Diclegis®.Full Prescribing Information. Bryn Mawr, PA: Duchesnay USA, Inc.; 2013.
2. Data on file. Duchesnay USA, Inc.

Table 2. Single-dose pharmacokinetics of the dual release combination of doxylamine- pyridoxine in healthy premenopausal, non-pregnant adult women

		DUAL RELEASE COMBINATION Mean ± SD				
		AUC_{0-t} (ng•h/mL)	**AUC_{0-inf} (ng•h/mL)**	**AUC_{0-72} (ng•h/mL)**	**C_{max} (ng/mL)**	**T_{max}[b] (h)**
Doxylamine	**N=48**	1367.0 ± 356.7	1425.8 ± 405.1	---	92.3 ± 15.7	4.5 (2.5-5.5)
Pyridoxine	**N=47**	42.3 ± 14.7	42.5 ± 14.7	---	47.1 ± 18.7	0.5 (0.5-4.7)
Pyridoxal[a]	**N=48***	203.7 ± 51.7	233.6 ± 55.9	---	58.9 ± 17.0	3.0 (0.8-5.0)
Pyridoxal 5′-phosphate[a]	**N=48**	---	---	1076.2 ± 382.2	30.1 ± 9.2	9.0 (3.0-16.0)

*N=46 for AUC_{0-inf}
[a] Baseline corrected values
[b] Median (range)

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Table 3. Multiple-dose pharmacokinetics of the dual release combination of doxylamine- pyridoxine given twice daily in healthy premenopausal, non-pregnant adult women

		DUAL RELEASE COMBINATION (Mean ± SD)				
		AUC_{0-24} (ng•h/mL)	**AUC_{0-12} (ng•h/mL)**	**AUC_{0-6} (ng•h/mL)**	**C_{max} (ng/mL)**	**T_{max} (h)**
Doxylamine	**N=34**	2879.4 ± 696.0	1573.2 ± 406.5	883.6 ± 228.5	173.6 ± 45.5	3.5 (1.0-20.0)
Pyridoxine	**N=34**	80.0 ± 22.7	46.3 ± 15.4	45.3 ± 16.3	48.2 ± 23.7	1.5 (0.3-16.5)
Pyridoxal[a]	**N=34**	1511.3 ± 300.0	848.1 ± 183.6	647.2 ± 149.6	189.6 ± 48.3	3.0 (2.0-15.0)
Pyridoxal 5′-phosphate[a]	**N=34**	1742.3 ± 554.3	831.7 ± 274.5	426.2 ± 144.0	85.9 ± 26.2	15.0 (2.0-24.0)

[a] Baseline corrected values
[b] Median (range)

Table 4 –Pharmacokinetics of doxylamine and pyridoxine metabolites following a single dose administration of the dual release combination under fed and fasted conditions in healthy premenopausal adult women

		Dual Release combination (N=23)				
		AUC_{0-t} (ng•h/mL)	**AUC_{0-inf} (ng•h/mL)**	**C_{max} (ng/mL)**	**$T_{max}^{b,c}$ (h)**	**$T_{1/2el}$ (h)**
Doxylamine Mean ± SD	**Fasted**	1273.7 ± 276.2	1321.9 ± 315.5	85.9± 10.6	3.5 (2.5-5.5)	11.9 ± 2.2
	Fed	1242.8 ± 254.0	1281.4 ± 282.9	64.5 ± 15.2	6.5 (2.0 – 24.0)	12.7 ± 2.60
Pyridoxine Mean ± SD	**Fasted**	34.7 ± 10.6	35.1 ± 8.5	38.9 ± 19.3	0.8 (0.3-4.3)	0.4 ± 0.2
	Fed	22.8 ± 9.9	27.0 ± 10.1	12.7 ± 5.7	8.0 (1.0 – 21.0)	1.2 ± 2.4
Pyridoxal[a] Mean ± SD	**Fasted**	209.4 ± 30.0	244.0 ± 32.5	62.0 ± 17.8	2.3 (0.8-5.0)	8.0 ± 1.7
	Fed	204.2 ± 25.7	249.2 ± 43.0	33.1 ± 6.1	6.0 (1.0-21.0)	12.5 ± 7.6
Pyridoxal 5′-phosphate[a] Mean ± SD	**Fasted**	1021.7 ± 318.5	---	27.4 ± 7.7	5.0 (3.0-71.8)	---
	Fed	1064.6 ± 386.9	---	30.2 ± 10.0	16.0 (6.0-22.0)	---

[a] Baseline corrected values
[b] Profile of Subject 20 was excluded
[c] Median (range)

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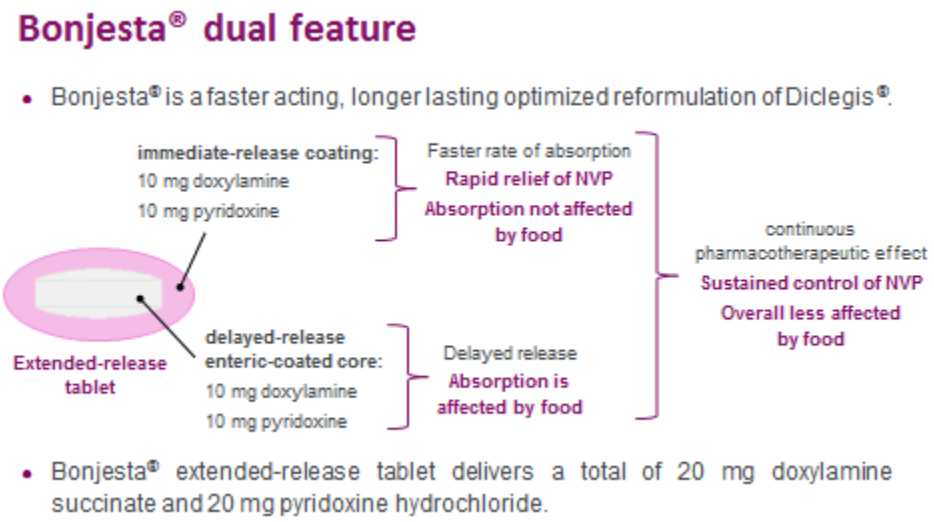

Figure 1: The structure- function of The dual release combination of doxylamine pyridoxine

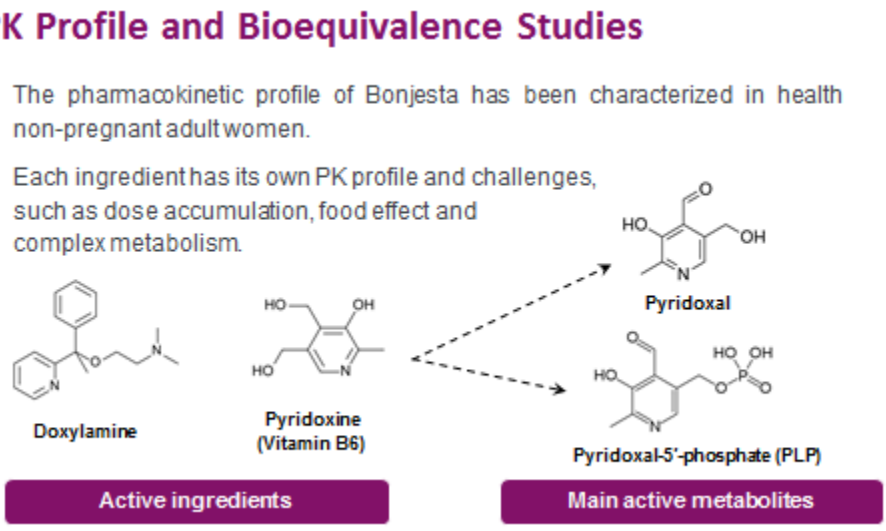

Figure 2: The active pharmacological ingredients of the dual release combination of doxylamine- pyridoxine

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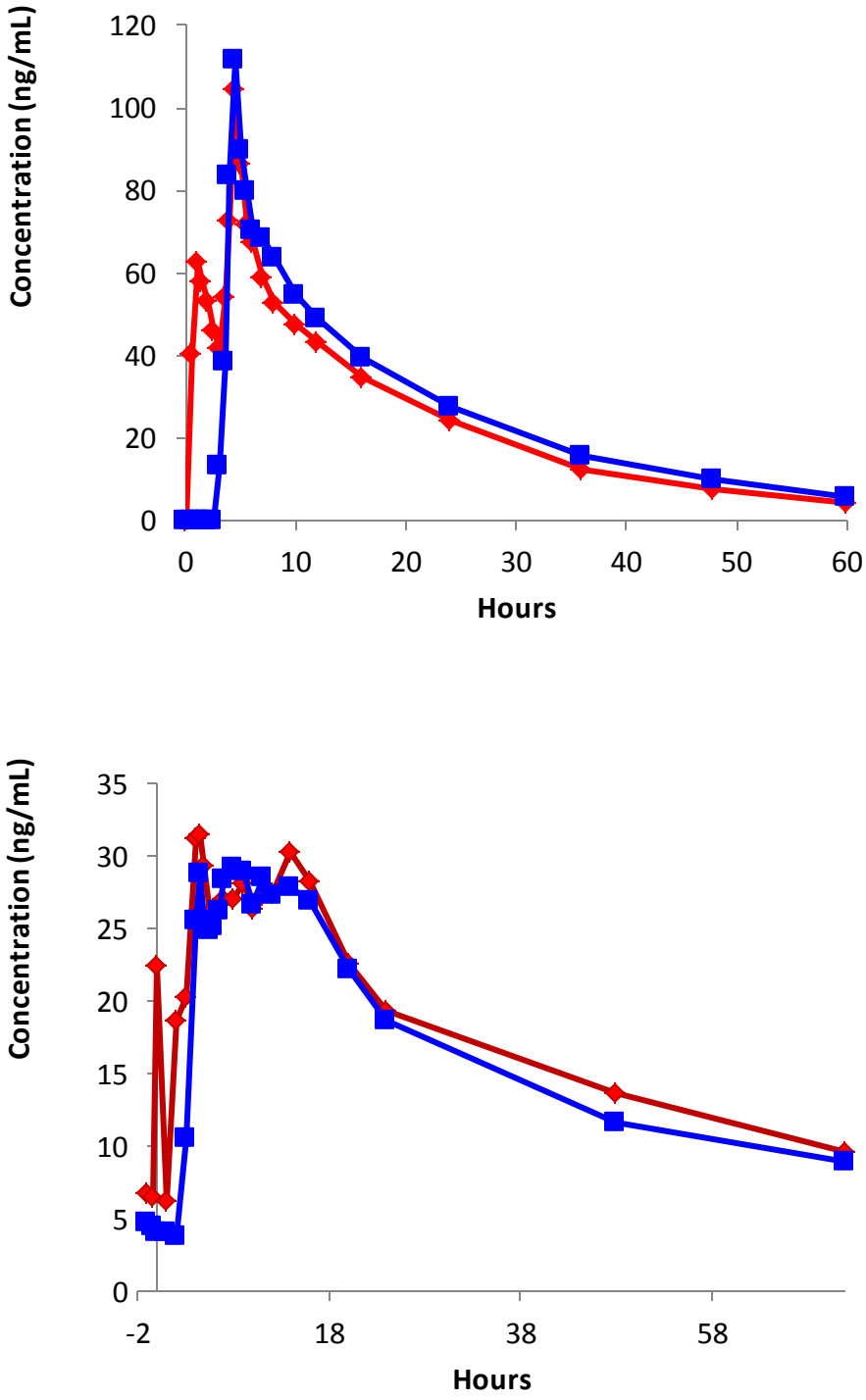

Figure 3: The dual release combination: Mean (± SD) concentration-time profile for doxylamine (upper pannel) and pyridoxal 5'-phosphate (lower pannel) in the single-dose bioequivalence study, from a representative patient (red = Dual release; blue = Delayed release)[41]

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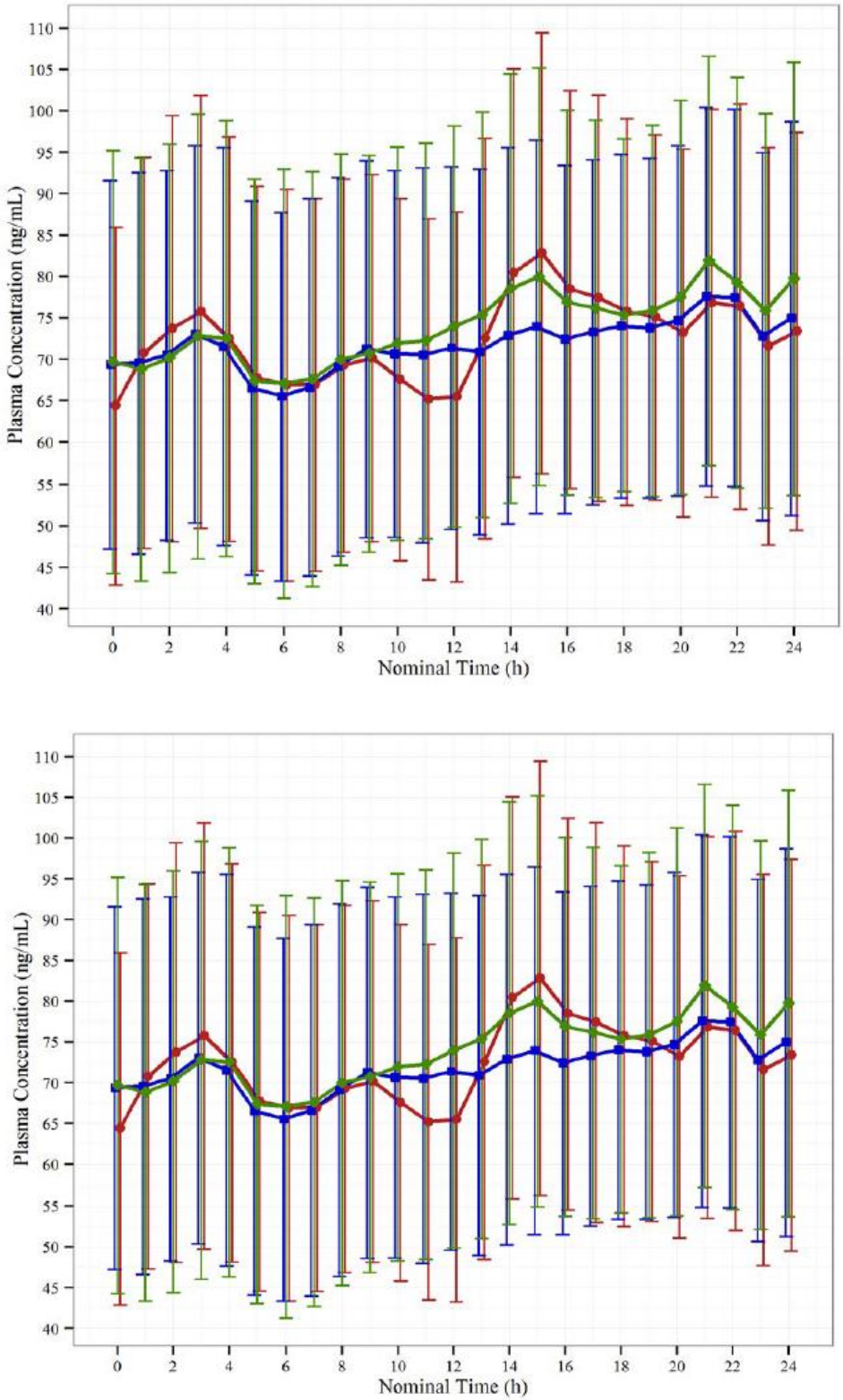

Figure 4: Mean (± SD) concentration-time profile for doxylamine (top) and pyridoxal 5'-phosphate (bottom) on Day 11 in the multiple-dose bioequivalence study (red = Dual release; blue and green are the Delayed release reference arms).[41]

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