PRODUCT MONOGRAPH

Vitamin-Mineral Supplement Tablets
For Prenatal/Postpartum Use

DIN 02246067

Vitamin-Mineral Supplement Tablets
High Dose Folic Acid for Prenatal Use
DIN 02276194

Multivitamins and other Minerals Including Combinations

Duchesnay Inc.
2925 boul. Industriel
Laval, Quebec
Canada, H7L 3W9
duchesnay.com

Date of Revision:
January 7, 2009

Submission Control Number: 121647 - 121649

Table of Contents

[Pr]PregVit®
Prenatal/Postpartum Vitamin-Mineral Supplement

[Pr]PregVit folic 5®
Prenatal High Dose Folic Acid Vitamin-Mineral Supplement

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – PregVit® and PregVit folic 5® Summary Product Information

Route of Administration	Dosage Form / Strength			Clinically Relevant Nonmedicinal Ingredients
Oral	***Each pink (a.m.) tablet contains (organized alphabetically)***	**[Pr]PregVit®**	**[Pr]PregVit folic 5®**	None *For a complete listing, see Dosage Forms, Composition and Packaging section.*
	Beta-Carotene (source of vitamin A)	2700 IU	2700 IU	
	Vitamin B_1 (thiamine mononitrate)	3 mg	3 mg	
	Vitamin B_2 (riboflavin)	3.4 mg	3.4 mg	
	Niacinamide	20 mg	20 mg	
	Pantothenic Acid (calcium pantothenate)	5 mg	5 mg	
	Vitamin B_6 (pyridoxine HCl)	10 mg	10 mg	
	Vitamin C (ascorbic acid)	120 mg	120 mg	
	Vitamin E (dl-alpha tocopheryl acetate)	30 IU	30 IU	
	Copper (cupric oxide)	2 mg	2 mg	
	Iodine (potassium iodide)	0.15 mg	0.15 mg	
	Iron (ferrous fumarate)[a,b,*]	35 mg	35 mg	
	Magnesium (magnesium oxide)	50 mg	50 mg	
	Zinc (zinc oxide)	15 mg	15 mg	
	Each blue/dark blue (p.m.) tablet contains			None *For a complete listing, see Dosage Forms, Composition and Packaging section*
	Folic Acid[b]	1.1 mg	5 mg	
	Vitamin B_{12} (cyanocobalamin)	12 µg	12 µg	
	Vitamin D_3 (cholecalciferol)	250 IU	250 IU	
	Calcium (calcium carbonate)[a,*]	300 mg	300 mg	

[a.] The purpose of taking the two tablets at different times is to prevent calcium inhibition on the absorption of iron.[1]
[b.] The purpose of taking the two tablets at different times is to prevent folic acid from interacting with iron resulting in their decreased intestinal absorption.[3]
[*] Elemental amount as iron from ferrous fumarate; as calcium from calcium carbonate.

INDICATIONS AND CLINICAL USE

PregVit® is a vitamin-mineral supplement specially formulated for use in women at least 2-3 months prior to conception[4] throughout pregnancy and during the postnatal period. PregVit folic 5® is a prenatal high dose folic acid vitamin-mineral supplement formulated for use in women who are planning pregnancy or pregnant and have had a previous pregnancy affected by a neural tube defect (NTD), women who have a family history of neural tube defects,[4, 6, 7, 8] have diabetes or malabsorption disorders,[5] (e.g., inflammatory bowel disease), who are taking folic acid antagonists (e.g., methotrexate) or anticonvulsant drugs (e.g., carbamazepine, phenobarbital, phenytoin, primidone, valproic acid),[6] or require a high dose folic acid supplement in the opinion of their physician.[7] Women are to take one pink (a.m.) and one dark blue (p.m.) PregVit folic 5® tablet daily at least 2-3 months prior to conception,[4] continuing up to 10 to 12 weeks after the last menstrual period, or throughout pregnancy, if, in the judgment of the attending physician, the benefits of continued high dose folic acid supplementation outweigh potential risks.

Women who have poor folate status from multifactorial dietary and environmental conditions, including poor eating habits, stringent dieting for weight loss, drug and alcohol abuse, and cigarette smoking should discuss folate supplementation with their physician.[7, 8]

Oral contraceptive users may also have lower folate concentrations than non-users as estrogen and progesterone could lower plasma and erythrocyte folate levels. Supplementation with folic acid may theoretically reduce the occurrence of maternal folic acid deficiency.

The physiological changes of pregnancy call for extra nutrients and energy to meet demands of an expanding blood supply, the growth of maternal tissues, a developing fetus, loss of maternal tissues at birth and preparation for lactation. During pregnancy, special attention should be given to folate, calcium, vitamin D and iron intakes because there is a potential for inadequate intakes in some groups of women.

Taking vitamin and mineral supplements does not eliminate the need for a balanced nutrition.

PregVit® and PregVit folic 5® are both formulated as two tablets in order to optimize the absorption of iron, calcium and folic acid; one pink (a.m.) tablet (with iron) is to be taken in the morning and a distinctly different blue/dark blue (p.m.) tablet (with calcium and folic acid) is to be taken in the evening. The rationale for this two tablet approach is to enhance bioavailability of iron; adjust the iron content so that it reduces adverse effects such as nausea, constipation, fatigue, diarrhea and headache associated with supplements containing higher levels of iron (60 mg) and; therefore increase compliance to the PregVit® and PregVit folic 5®. Calcium is provided separately from iron to avoid calcium inhibition of iron absorption from the gastrointestinal tract.[1, 2] A higher dose of vitamin C is also present in the morning tablet to facilitate iron absorption.[9, 10] Manganese was purposely excluded from these tablets so as not to affect iron absorption.[9, 11]

Concurrent ingestion of folic acid and iron may result in the formation of stable complexes.[3] Folic acid is provided separately from iron to prevent their decreased intestinal absorption.

CONTRAINDICATIONS

These products are contraindicated in patients with known hypersensitivity to any of the ingredients in the formulation or component of the container. *For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.*

WARNINGS AND PRECAUTIONS

General

Although it has been suggested that high doses of folate may mask manifestations of vitamin B_{12} deficiency, a study by Metz et al. (2004) could not demonstrate that high serum folate levels masked the macrocytosis of cobalamin deficiency whether the serum folate was low, normal or high.[12]

To address potential concerns regarding the masking of vitamin B_{12} deficiency and the potential precipitation or exacerbation of the progression of neurological complications associated with vitamin B_{12} deficiency, the use of folic acid in conjunction with vitamin B_{12} as a supplement should be recommended.[13] Vitamin B_{12} levels may be monitored if, in the opinion of the healthcare professional, it is warranted.

Keep this product out of the reach of children. Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. In case of accidental overdose, call a regional poison control centre immediately (See OVERDOSAGE).

Do not exceed the recommended dose.

Dependence/Tolerance

There is no information to indicate that abuse or dependency occurs at the concentration of vitamins and minerals found in PregVit® and PregVit folic 5®.

Hematologic

Folic acid should be used in conjunction with vitamin B_{12} in order to avoid potential neurologic complications. Any dose of folic acid over 1 mg per day may require monitoring for vitamin B_{12} deficiency by a healthcare provider.

Neurologic

Women with seizure disorders controlled on anticonvulsant medications (e.g., carbamazepine, phenobarbital, phenytoin, primidone, valproic acid) may have exacerbation of seizures when folic acid is taken.[4, 26, 30]

Special Populations

Pregnant Women:

Although the use of a folic acid supplement during the periconceptional period reduces the number of NTDs, they cannot be completely avoided through folate supplementation due to their multifactorial origin.

Taking vitamin and mineral supplements does not eliminate the need for a balanced nutrition.

Baseline Risk:
The background baseline risk of major malformations for all pregnancies is approximately 1-3%. This is the risk of having a child with a birth defect when no teratogenic exposure occurs in pregnancy. This underlying risk may be increased due to maternal age, medical or family history, or exposures to certain drugs, chemicals or levels of radiation known to cause birth defects.

Each year, a quarter of a million pregnancies worldwide result in the birth of an infant with a neural tube defect (NTD) or an abortion performed because of such effect.[8] In a recent study, a total of 2446 subjects with NTDs were recorded among 1.9 million births from 1993 to 2002 in seven Canadian provinces. The prevalence of NTDs was 0.86 per 1000 births.[14]

Nursing Women:
PregVit® is specifically indicated in the postpartum period. The decision to continue use of PregVit folic 5® during lactation should be made by a healthcare professional.

The passage of vitamins and minerals into breast milk can be expected. Folic acid is actively excreted into breast milk. Accumulation of folate in milk takes precedence over maternal folate needs. Levels of folic acid are relatively low in colostrum but as lactation proceeds, concentrations of the vitamin rise. Folate levels in newborns and breast-fed infants are consistently higher than those in mothers and normal adults. In Japanese mothers, mean breast milk folate concentrations were 141.4 ng/mL, resulting in a total intake by the infant of 14-25 μg/kg/day. Much lower mean levels were measured in pooled human milk in an English study examining preterm (26 mothers, 29-34 weeks) and term (35 mothers, 39 weeks or longer) patients. Preterm milk folate concentrations rose from 10.6 ng/mL (colostrum) to 30.5 ng/mL post-natal (16-196 days), whereas term milk folate concentrations increased during the same period from 17.6 to 42.3 ng/mL.[15]

In one study, maternal serum and red blood cell folate levels increased significantly after 1 mg of folic acid/day for 4 weeks, but milk folate levels remained unchanged. Investigators gave well-nourished lactating women a multivitamin preparation containing 0.8 mg of folic acid. At 6 months postpartum, milk concentrations of folate did not differ significantly from those of controls who were not receiving supplements. Other investigators measured more than adequate blood folate levels in American breast-fed infants during the 1st year of life. The mean milk concentration of folate consumed by these infants was 85 ng/mL.[15]

In a study of lactating mothers with megaloblastic anemia treated with 5 mg/day of folic acid for 3 days, breast milk folate rose from 7-9 ng/mL to 15-40 ng/mL 1 day after treatment began. The elevated levels were maintained for 3 weeks without further treatment. Nine lower-socioeconomic status women were treated with multivitamins containing 0.8 mg of folic acid and were compared with seven untreated controls. Breast milk folate was significantly higher in the treated women. In another study of lactating women with low nutritional status, supplementation with folic acid, 0.2-10.0 mg/day, resulted in mean milk concentrations of 2.3-5.6 ng/mL. Milk concentrations were directly proportional to dietary intake.[15]

Monitoring and Laboratory Tests

To address potential concerns that high doses of folate may mask manifestations of vitamin B_{12} deficiency, signs or symptoms of vitamin B_{12} deficiency should be considered before initiating folic acid supplementation if doses are greater than 1.0 mg. Vitamin B_{12} levels may be monitored before and during PregVit® and PregVit folic 5® therapies if in the opinion of the healthcare professional it is warranted.

Monitor folate level when drugs known to interact with folic acid are taken concomitantly (See Table 2, DRUG INTERACTIONS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Allergic sensitization has been reported following both oral and parenteral administration of folic acid.

At high doses (e.g. 15 mg/day) folic acid has been associated on rare occasion with various gastrointestinal symptoms and CNS effects such as sleep disturbances, difficulty concentrating, irritability, hyperactivity, excitement, mental depression, confusion, and impaired judgment.[16] In general, adverse reactions associated with iron supplements whether alone or in a multivitamin are: constipation, nausea, fatigue, diarrhea and headache.[17, 18, 19]

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

A randomized, crossover open labelled study in 138 pregnant women attending outpatient clinics was conducted to compare tolerability and compliance with PregVit® (a.m. and p.m. tablets) versus a supplement with high iron content in pregnant women.[20] An equal number of pregnant women suffering from nausea and vomiting of pregnancy (NVP) and pregnant women without NVP were randomized to receive either PregVit® or a supplement with high iron content for one month. The primary end point of interest was the mean rate of adverse events including decreased compliance. The mean rate of adverse event was collected for nausea, constipation and other adverse drug events and is illustrated in Table 2. Incidence of nausea was approximately 9% in PregVit® group versus 10% in the supplement with high iron content group (p=0.71); incidence of constipation was 22.5% in PregVit® group versus 34.8% in the supplement with high iron content group (p=0.03) and for other adverse events, the average number of events was 10.4 for the PregVit® group versus 9.9 for the supplement with high iron content group (p=0.95).[20]

Table 2 - Overall study results, comparing PregVit® (low iron) to a supplement with a high iron content over a month administration in a cross-over design.

Adverse events (n=138)	PregVit® (SD)	Supplement with high iron content (SD)	p value
Adverse events (%)	17.6 ± .24	20.3 ± 24	0.14
Nausea (%)	9.3 ± 19	10.1 ± 18	0.71
Constipation time length (%)	3.1 ± 8	4.7 ± 11	**0.05**
Other adverse events	10.4 ± 21	9.9 ± 20	0.95
Nausea rate (%)	41.3 (57/81)	45.7 (63/75)	0.54
Constipation Rate (%)	22.5 % (31/107)	34.8 % (48/90)	**0.03**

In a single-dose crossover pharmacokinetic study conducted with the PregVit® blue (p.m.) tablet in 6 healthy non-pregnant women (18-45 years), no adverse reactions were reported.[21]

In another study of similar design, 12 healthy women were administered high iron and calcium and low iron without calcium [PregVit® pink (a.m.) tablet] separately on two different occasions. No adverse reactions were reported.[9]

Abnormal Hematologic and Clinical Chemistry Findings

None reported.

Post-Market Adverse Drug Reactions

PregVit® and PregVit folic 5® have the same medicinal ingredients and strengths with the exception of the amount of folic acid (1.1 mg vs. 5 mg). Spontaneous adverse reactions reported for these products are summarized in Table 3.[22, 23] Reactions are presented by MedDRA System Organ Class (SOC) and Preferred Terms (signs, symptoms and diagnosis) from spontaneous notification.

Table 3 - Cumulative summary of PregVit® and PregVit folic 5® adverse reactions from spontaneous reports to Duchesnay Inc. and regulatory authority (Health Canada) from launching date to September 30th, 2008.

MedDRA Preferred Term	PregVit® Spontaneous Reports	PregVit folic 5® Spontaneous Reports
SOC: Eye disorders (n=2)		
Eye pruritus	1	0
Visual impairment	0	1
SOC: Gastrointestinal disorders (n=45)		
Nausea	10	4
Vomiting	8	1
Constipation	3	0
Diarrhea	3	0
Stomach discomfort	2	1
Abdominal pain upper	2	0
Dyspepsia	2	0
Abdominal distension	1	1
Infrequent bowel movement	1	1
Chelitis	1	0
Heartburn	1	0
Lip dry	1	0
Retching	1	0
Abdominal pain lower	0	1
SOC: General disorders and administration site conditions (n=7)		
Feeling abnormal	2	0
Asthenia	1	0
Fatigue	1	0
Hunger	1	0
Pyrexia	1	0
Thirst	1	0
SOC: Metabolism and nutrition disorders (n=4)		
Decreased appetite	2	0
Dehydration	1	0
Hyperglycemia	1	0

Table 3- Cumulative summary of PregVit® and PregVit folic 5® adverse reactions from spontaneous reports to Duchesnay Inc. and regulatory authority (Health Canada) from launching date to September 30th, 2008. (cont'd)

SOC: Musculoskeletal and connective tissue disorders (n=1)		
Myalgia	1	0
SOC: Nervous system disorders (n=5)		
Headache	1	1
Dizziness	1	0
Lethargy	1	0
Migraine	0	1
SOC: Pregnancy, puerperium and perinatal conditions (n=2)		
Vomiting in pregnancy	2	0
SOC: Psychiatric disorders (n=4)		
Insomnia	2	1
Nervousness	1	0
SOC: Renal and urinary system disorders (n=5)		
Chromaturia	3	2
SOC: Respiratory and thoracic disorders (n=2)		
Dyspnea	1	0
Throat tightness	1	0
SOC: Skin and subcutaneous tissue disorders (n=2)		
Urticaria	1	0
Rash macular	0	1

DRUG INTERACTIONS

Overview

No formal vitamin/mineral-drug interaction studies have been performed with PregVit® or PregVit folic 5®.

Iron supplements may decrease absorption of thyroid hormone medications.[24] Therefore, iron supplements whether alone or as part of a prenatal supplement, should not be taken at the same time as levothyroxine or other thyroid hormone medications (Synthroid®, Eltroxin®, Levo-T®, Levothroid®, Levoxyl®, Euthroid®, Thyrolar®, etc.). Allow at least four (4) hours between taking iron and thyroid hormones.[24] Calcium can also interfere with the absorption of thyroid drugs.[24] Allow at least four (4) hours between taking calcium and thyroid hormones.

Due to the inhibitory effect of calcium on iron absorption, women should be encouraged to take these supplements at different time. A high intake of iron can interfere with zinc absorption therefore; 15 mg of supplemental zinc should be taken when elemental iron supplementation exceeds 30 mg per day. When supplemental zinc is taken, concurrent supplementation with 2 mg copper is advised.[25]

Concurrent ingestion of folic acid and iron may result in the formation of stable complexes with iron, resulting in their decreased intestinal absorption.[3]

Several other drugs have reduced bioavailability when ingested with iron preparations. These include carbidopa, ciprofloxacin, levodopa, methyldopa, penicillamine, tetracyclines.[3] A large number of drugs form stable complexes with iron, however, little is known about the clinical consequences of this binding. Further investigation is required to determine the clinical interactions between iron and drug molecules.

Drugs including, antibiotic therapies, bisphosphonates, carbidopa, fluoroquinolone antibiotics, levodopa, methyldopa and penicillamine should be taken at least two (2) hours apart from PregVit® and PregVit folic 5®.

Drugs including, cholestyramine, colestipol, levothyroxine and mycophenolate mofetil should be taken at least four (4) hours apart from PregVit® and PregVit folic 5®.

Vitamin/Mineral-Drug Interactions

Table 4 - Vitamin/Mineral- Drug Interactions for PregVit® and PregVit folic 5®

Vitamin/Mineral	Drugs	Effect	Clinical comment
Folic Acid	Antacids	Can reduce folic acid absorption.[26]	
	Antibiotic therapy	Can disrupt the normal gastrointestinal (GI) flora, interfering with absorption of folic acid.[26]	
	Antiepileptic drugs (carbamazepine, phenobarbital, phenytoin, primidone, valproic acid)	Antiepileptic drugs can reduce serum folate levels, occasionally leading to megaloblastic anemia. Folic acid supplements have also decreased seizure control in some people with epilepsy.[26]	Seizure activity should be monitored closely. Monitor folate levels, particularly in pregnant women, who are at risk of reduced folate.[26]
	Chloramphenicol	May antagonize some effects of folic acid on the blood (hematopoietic system).[26]	
	Cholestyramine	When administered together, there may be reduction or delay in folic acid absorption.[26]	If concomitant therapy is required, folic acid should be administered at least one (1) hour before or four (4) to six (6) hours after cholestyramine.[26]

Vitamin/Mineral	Drugs	Effect	Clinical comment
Folic Acid (cont'd)	Colestipol	Can interfere with absorption of folic acid, and reduced serum folate levels may occur.[26]	
	Dihydrofolate reductase inhibitors (sulphasalazine, triamterene, trimethoprim)	Inhibit absorption and metabolism of folic acid.[26]	Monitor serum and red blood cell folate levels.[26]
	H2 blockers (cimetidine, famotidine, nizatidine, ranitidine) and Proton Pump Inhibitors (esomeprazole, iansoprazole, omeprazole, pantoprazole, rabeprazole)	Folic acid absorption from the small intestine is optimal at pH 5.5 to 6. The increased pH associated with H2 blockers may therefore reduce folic acid absorption.[26]	Monitor for folate deficiency.[26]
	Malaria drugs (sulfadoxine-pyrimethamine)	Prevents conversion of folic acid to its active form.[26]	Monitor for folate deficiency.[26]
	Methotrexate	Methotrexate is a folate antagonist which prevents conversion of folic acid to its active form, and lowers plasma and red blood cell folate levels.[26]	Monitor for folate deficiency.[26]
	NSAIDs (ibuprofen, indomethacin, naproxen, sulindac)	Folate-dependent enzymes have been inhibited in laboratory experiments by certain NSAIDs.[26]	Monitor for folate deficiency.[26]
	Pancreatic extracts (Cotazym®, Creon®, Pancrease®, Ultrase®, Viokase®)	May possibly reduce folic acid absorption.[26]	Folate levels should be checked in patients taking pancreatic enzymes for prolonged periods.[26]
	Pyrimethamine	Pyrimethamine is a folate antagonist that prevents conversion of folic acid to its active form.[26]	Monitor for folate deficiency.[26]
Iron	Acetohydroxamic acid	Iron supplements may cause medication to be less effective.[27]	
	Allopurinol	May cause an increase in iron storage in the liver.[27]	Do not use allopurinol with iron supplements.[27]
	Aminosalicylic acid	May cause malabsorption syndrome (including iron depletion).[27]	
	Antacids	May reduce iron absorption and reduce efficacy.[27]	Separate the doses of antacids and iron.[27]

Vitamin/Mineral	Drugs	Effect	Clinical comment
Iron (cont'd)	Antibiotic therapy (doxycycline, methacycline, oxytetracycline, tetracycline)	Forms iron-drug complexes reducing the extent of drug absorption.[27]	It is recommended to take iron supplements and these drugs at least two (2) hours apart.[27]
	Aspirin and NSAIDs	Can cause mucosal damage and bleeding throughout the gastrointestinal tract. Chronic blood loss may contribute to iron deficiency. Iron supplements may also irritate the gastrointestinal tract.[27]	
	Bisphosphonates (alendronate, etidronate, risedronate, tiludronate)	Iron can decrease absorption of bisphosphonates by forming insoluble complexes.[27]	Take bisphosphonates and iron at least two (2) hours apart.[27]
	Carbidopa, levodopa	Forms iron-drug complexes reducing the extent of drug absorption.[27]	It is recommended to take iron supplements and these drugs at least two (2) hours apart.[27]
	Chloramphenicol	Can reduce the response to iron therapy in iron deficiency anemia.[27]	
	Cholestyramine, colestipol	May bind iron in the gut, reducing its absorption.[27]	Take cholestyramine or colestipol at least four (4) hours apart.[27]
	Fluoroquinolone antibiotics (ciprofloxacin, levofloxacin, ofloxacin)	Iron decreases absorption of fluoroquinolone antibiotics.[27]	Take fluoroquinolone antibiotics and iron at least two (2) hours apart.[27]
	H2 blockers (cimetidine, ranitidine, famotidine, nizatidine) and Proton Pump Inhibitors (esomeprazole, iansoprazole, omeprazole, pantoprazole, rabeprazole)	Gastric acid is important for the absorption of iron.[27]	
	Levothyroxine (e.g. Synthroid) (Please also see Calcium-Levothyroxine interaction)	Iron reduces the absorption of thyroid hormones.[27]	It is recommended to take iron supplements and levothyroxine at least four (4) hours apart.[24] Thyroid levels should be monitored regularly during pregnancy and in the first few months postpartum.[24]
	Methyldopa	Forms iron-drug complex reducing the extent of drug absorption.[27]	It is recommended to take iron supplements and methyldopa at least two (2) hours apart.[27]

Vitamin/Mineral	Drugs	Effect	Clinical comment
Iron (cont'd)	Mycophenolate mofetil	Iron can markedly reduce absorption of mycophenolate mofetil.[27]	Iron should be taken at least four (4) to six (6) hours before, or two (2) hours after mycophenolate mofetil.[27]
	Pancreatic enzymes (Pancrease®, Cotazym®, Viokase®, Creon®, Ultrase®)	Can reduce iron absorption, possibly by binding iron or altering pH.[27]	
	Penicillamine	Forms iron-drug complex reducing the extent of drug absorption.[27]	It is recommended to take iron supplements and penicillamine at least two (2) hours apart.[27]
Calcium	Levothyroxine (e.g. Synthroid) (Please also see Iron-levothyroxine interaction)	Calcium supplements reduce the effectiveness of levothyroxine.[24]	It is recommended to take calcium supplements and levothyroxine at least four (4) hours apart.[24] Thyroid levels should be monitored regularly during pregnancy and in the first few months postpartum.[24]
	Tetracycline	Calcium interferes with absorption of tetracycline.[28]	It is recommended to take tetracycline one (1) hour before or two (2) hours after calcium supplements.[28]

Vitamin/Mineral-Food Interactions

Interactions with food have been established with iron and calcium.

Iron

Factors that enhance non-heme iron absorption include: meat, poultry, fish and vitamin C.[1]
Factors that inhibit non-heme iron absorption include: polyphenols in tea, coffee; phytate in legumes, soybeans, whole grains; oxalate in spinach, chard, beet greens, rhubarb, sweet potato and calcium in both food and supplements.[1]

Due to the inhibitory effect of calcium on iron absorption, women should be encouraged to take these supplements at different times.[1]

Calcium

Compounds such as oxalate and phytate reduce calcium absorption.[1] These compounds are found in foods such as legumes, grains, spinach, chard, beet greens, sweet potatoes and rhubarb.

Absorption of calcium carbonate can be improved when food has increased gastric acid levels.[2]

Vitamin/Mineral-Vitamin/Mineral interactions

Vitamin/mineral-vitamin/mineral interactions are important for the PregVit® and PregVit folic 5® formulations, the dosing regimen itself [pink a.m. and blue/dark blue p.m. tablets at least four (4) hours apart] as well as the timing of administration of external sources of vitamins and minerals.

Concurrent ingestion of folic acid and iron may result in the formation of stable complexes with iron, decreasing their intestinal absorption.[3] Vitamin C is known to increase the absorption of iron.[9, 10] Calcium has an inhibitory effect on iron absorption. Manganese also interferes with iron absorption.[9, 11] Vitamin D metabolites enhance calcium absorption.[2]

These same interactions are seen with external sources of vitamins and minerals including supplements.

High intake of iron can interfere with zinc absorption. For this reason, 15 mg per day supplemental zinc should be taken when elemental iron supplementation exceeds 30 mg per day. When supplemental zinc is taken, concurrent supplementation with 2 mg copper is advised.[25]

Table 5 - Vitamin/Mineral - Vitamin/Mineral Interactions for PregVit® and PregVit folic 5®

Vitamin/Mineral	Vitamin/mineral	Effect	Clinical comment
Folic Acid	Iron	Forms stable complexes with iron and decreases intestinal absorption of iron.	Take at different times in the day.
Iron	Zinc	Iron inhibits absorption of zinc.	Take 15 mg per day supplemental zinc when elemental iron supplementation exceeds 30 mg per day. When supplemental zinc is taken, concurrent supplementation with 2 mg copper is advised.[25]
	Manganese	Inhibits absorption of iron.	
	Vitamin C	Facilitates iron absorption.	
Calcium	Iron	Calcium inhibits absorption of iron.	Take at different times in the day.
	Vitamin D	Vitamin D metabolites enhance calcium absorption.	

Vitamin/Mineral-Herb Interactions
Interactions with herbal products have not been established.

Vitamin/Mineral-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

For PregVit® or PregVit folic 5® take one pink (a.m.) tablet  in the morning and one blue/dark blue (p.m.) tablet  in the evening at least four (4) hours apart. The purpose of taking the two tablets at different times is to prevent calcium inhibition on the absorption of iron[1, 2] and to prevent folic acid from interacting with iron resulting in their decreased intestinal absorption.[3]

For PregVit®, take at least 2-3 months prior to conception,[4] throughout pregnancy and during the postnatal period.

For PregVit folic 5® take at least 2-3 months prior to conception, continuing up to 10-12 weeks after last menstrual period, or throughout pregnancy, if, in the judgment of the attending physician, the benefits of continued high dose folic acid supplementation outweigh potential risks.

It is preferable to take the PregVit®/PregVit folic 5® pink (a.m.) tablet on an empty stomach with a glass of water and to wait at least one (1) hour before taking any food to optimize iron absorption, and to take the PregVit®/PregVit folic 5® blue/dark blue (p.m.) tablet within one (1) hour of an evening meal to optimize calcium absorption.

The schedule may be individualized according to a woman's specific condition:

- For *women taking calcium rich food for breakfast*, the PregVit®/PregVit folic 5® **pink (a.m.)** tablet may be taken two (2) hours or more after breakfast. Following administration of the **pink (a.m.)** tablet a wait of one (1) additional hour is recommended before eating in order to optimize the absorption of iron.
- For *women suffering from nausea and/or vomiting* <u>*in the morning*</u> where it is difficult to take vitamin-mineral supplements on an empty stomach, the PregVit®/PregVit folic 5® **pink (a.m.)** tablet may be taken two (2) hours or more after breakfast. Following administration of the **pink (a.m.)** tablet a wait of one (1) additional hour is recommended before eating in order to optimize the absorption of iron.
- For *women taking levothyroxine hormone in the morning*, it is recommended to take the PregVit®/PregVit folic 5® **pink (a.m.)** tablet at least four (4) hours apart to optimize the absorption of *levothyroxine hormone*. For *women taking levothyroxine hormone at bedtime*, it is recommended to take the PregVit® **blue (p.m.)** or PregVit folic 5® **dark blue (p.m.)** tablet at least four (4) hours apart to optimize the absorption of *levothyroxine hormone*.

There is no specific recommendation to support a different dosage of vitamin-mineral supplement in *multiple pregnancies*.

<u>Missed Dose</u>

When a dose has been missed, it should be taken as soon as possible: one pink (a.m.) and one blue/dark blue (p.m.) tablets should be taken within a 24 hour period. It is recommended that PregVit®/PregVit folic 5® pink (a.m.) and blue/dark blue (p.m.) tablets be taken at least four (4) hours apart in order to optimize the absorption of nutrients.

The prescribed dosing schedule should then continue as directed by physician or healthcare professional.

<u>Administration</u>

PregVit®/PregVit folic 5® tablets are to be taken orally.

Tablets are not intended to be crushed or split. No stability and absorption data is available for crushed or split PregVit®/PregVit folic 5® tablets.

OVERDOSAGE

For management of a suspected drug overdose, contact your **regional Poison Control Centre**.

Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6.

PregVit® and PregVit folic 5® are supplied in a 30-day blister pack containing 30 oval, pink (a.m.) tablets and 30 oval, blue/dark blue (p.m.) tablets. Each PregVit®/PregVit folic 5® pink (a.m.) tablet contains 35 mg of elemental iron. No iron is contained in the PregVit® blue (p.m.) tablet or PregVit folic 5® dark blue (p.m.) tablet. The amount of elemental iron in one box or a 30-day supply of PregVit®/PregVit folic 5® is 1050 mg.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PregVit®/PregVit folic 5® provide a supplement of vitamins and minerals in an immediate release dosage form. Administration of the pink (a.m.) and the blue/dark blue (p.m.) tablets at two different times helps to maximize the absorption of iron, calcium and folic acid.

Clinical Pharmacology

Folic acid, also known as folate, pteroylglutamic acid or vitamin B_9, is a water-soluble B complex vitamin. After absorption from the gastrointestinal tract, folic acid is converted in the liver to tetrahydrofolic acid, which is a cofactor in the biosynthesis of purines and thymidylates of nucleic acids. An exogenous source of folic acid is necessary for the synthesis of nucleoproteins and maintenance of normal erythropoiesis. There is strong evidence that prophylactic therapy with folic acid, prior to and during pregnancy, can reduce the risk of fetal neural tube defects (NTDs). NTDs result from improper development and closure of the neural tube during the third and fourth weeks of gestation. Pregnancies affected by a NTD may result in a miscarriage or stillbirth, and children born with a NTD may have mild to severe disability or die in early childhood. NTDs include spina bifida, anencephaly and encephalocele.

Although the use of a folic acid supplement during the periconceptional period reduces the number of NTDs, they cannot be completely avoided through folate supplementation because of their multifactorial origin. For women who had prior history of NTDs, the recurrence rate is 2-3%. Consuming 5 mg of folic acid daily has the potential of reducing the incidence of another NTD pregnancy by up to 72%, i.e., down to 1%.

There is evidence that an increase of 0.4 mg/day of folic acid would reduce the risk of neural tube defects for all women planning a pregnancy by about 36%, 1 mg per day would reduce the risk by about 57%, 1.1 mg per day would reduce the risk by about 59% and the use of a 5 mg tablet daily would reduce the risk by about 85%.[8]

Pharmacokinetics

PregVit® and PregVit folic 5® are both multivitamin-mineral preparations containing the same active ingredients in a pink (a.m.) and blue/dark blue (p.m.) tablet presentation. The pink (a.m.) tablets are exactly the same for both preparations. In the blue and dark blue (p.m.) tablets, the amount of folic acid is different: PregVit® blue (p.m.) tablets contain 1.1 mg of folic acid and PregVit folic 5® dark blue (p.m.) tablets contain 5 mg of folic acid.

The absorption of iron following the administration of PregVit®/PregVit folic 5® pink (a.m.) tablets was measured in twelve healthy, non-pregnant women. The area under the concentration-time curve (AUC) for serum iron was 79.1 ± 36.0 μM*h. Upon standardizing the AUC for dose, the relative absorption over the 8-hour time period was 2.3 ± 1.0 μM*h/mg.[9]

There is no evidence of circadian rhythm variation in folate pharmacokinetics. In a crossover design, six healthy, non-pregnant women were randomized to receive 1 PregVit® blue (p.m.) tablet, containing 1.1 mg of folic acid, in the morning or evening.[21] Serum folate levels were measured over 10 hours. The area under the concentration-time curve (AUC) was used to compare the extent of absorption between the two time periods. The mean AUC values for serum folate after administration of the PregVit® blue (p.m.) tablets were 334.5 ± 119.6 nM*h and 283.1 ± 64.3 nM*h for morning and evening, respectively (p=0.17). The morning and evening peak serum folate concentrations (Cmax) were also similar (135.3 ± 41.7 nM and 130.3 ± 14.2 nM, respectively) (p=0.75). There was no difference in the time to peak concentration (Tmax) for the morning (1 ± 0.5 hour) and the evening (1 ± 0.4 hour) administration. Folic acid contained in the PregVit® blue (p.m.) tablet was absorbed similarly whether administered in the morning or in the evening.

A study comparing folic acid pharmacokinetics was completed where serum folate levels of single dose PregVit® and PregVit folic 5® were measured pre-dose and up to 10 hours post dose in healthy non-pregnant fertile women between the ages of 18 and 45 years. The mean area under the curve (AUC) of 1.1 mg and 5 mg folic acid were 147.6 ± 52.8 (ng/mL)·hr and 997.5 ± 271.9 (ng/mL)·hr, respectively ($p<0.0002$). An approximate 5-fold difference was detected in the peak concentrations (Cmax) between the 2 groups ($p<0.0005$), alongside a slight difference in the times to peak (Tmax) ($p=0.02$). The estimated steady-state serum folate concentrations produced by 1.1 mg and 5 mg folic acid were 6.2 ± 2.2 ng/mL and 41.6 ± 11.3 ng/mL, respectively ($p<0.0002$), prior to its summation with initial (baseline) steady-state levels. Single dose administration between 1.1 mg and 5 mg folic acid demonstrated linear pharmacokinetics, with approximately a 5-fold difference between the 2 doses in serum folate contribution to steady-state levels, under ideal adherence.[32]

The study results are summarized in Table 6 below:

TABLE 6 - Single dose pharmacokinetic comparison of PregVit folic 5 (5 mg) versus PregVit (1.1 mg) folic acid ingestion, among non-pregnant women of childbearing age

	5 mg folic acid (n=6)	1.1 mg folic acid (n=6)	p-value (Student's t-test)
Baseline (fasting) serum folate concentration, at time=0 (ng/mL)	11.2 ± 3.9	13.2 ± 4.0	0.41
Area under the curve, AUC [(ng/mL)·hr]	997.5 ± 271.9	147.6 ± 52.8	<0.0002
$C_{max,}$ peak serum folate concentration (ng/mL)	273.3 ± 56.3	59.7 ± 18.4	<0.0005
T_{max}, time to achieve peak concentration (hr)	1.8 ± 0.4	1.2 ± 0.4	0.02
Apparent clearance (mL/min)	91.7 ± 37.2	143.6 ± 66.6	0.13
Estimated steady-state serum folate concentration produced by supplemental folic acid (ng/mL)	41.6 ± 11.3	6.2 ± 2.2	<0.0002
Overall estimated steady-state serum folate concentration¶ (ng/mL)	52.8 ± 12.6	19.3 ± 4.2	<0.0001

Note: Data presented as mean ± standard deviation

¶ Overall estimated steady-state serum folate concentration = baseline concentration + estimated steady-state serum folate concentration produced by supplemental folic acid.

Special Populations and Conditions

Race: No data is available on differences in the pharmacokinetics of either PregVit®/PregVit folic 5® pink (a.m.) or blue/dark blue (p.m.) tablet in different races.

Hepatic Insufficiency: No data is available on differences in the pharmacokinetics of either PregVit®/PregVit folic 5® pink (a.m.) or blue/dark blue (p.m.) tablet in patients with hepatic insufficiency.

Renal Insufficiency: No data is available on differences in the pharmacokinetics of either PregVit®/PregVit folic 5® pink (a.m.) or blue/dark blue (p.m.) tablet in renal insufficiency.

Genetic Polymorphism: No data is available on differences in the pharmacokinetics of either PregVit®/PregVit folic 5® pink (a.m.) or blue/dark blue (p.m.) tablet in patients with genetic polymorphism.

STORAGE AND STABILITY

Store at room temperature (15 to 30ºC).

Protect from moisture. Contact with moisture may produce surface discoloration or erosion of the tablet.

Keep in a safe place out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PregVit® and PregVit folic 5® are supplied in a 30-day blister pack containing 30 oval, pink (a.m.) tablets and 30 oval, blue/dark blue (p.m.) tablets.

Tablets are imprinted with the pink image of a pregnant woman.

The indicia of the pregnant woman serves as a method to diminish the concern over erroneous ingestion by pregnant women or erroneous dispensing by pharmacists of therapeutic agents not prescribed or labelled for pregnant women. Noncompliance in the use of prescription medications is common among pregnant women owing to fear over fetal exposure and safety even in the case of drugs with appropriate safety data.

An observational, prospective cross-sectional study was conducted by the manufacturer to determine the teratogenic risk perception of pregnant women when viewing a plain tablet and a tablet imprinted with the image of a pregnant woman. The difference in teratogenic risk perception was highly significant ($p<0.0001$). In the survey group of 132 pregnant women the mean perception of teratogenic risk was decreased by 23.4% when viewing tablets imprinted with the image of a pregnant woman. By reducing the perception of teratogenic risk by pregnant women the pregnancy indicia may increase patient compliance and thus the effectiveness of the treatment.[29]

Medicinal Ingredients:
Each oval shaped, pink (a.m.), film-coated, immediate release tablet contains:

	PregVit®	**PregVit folic 5®**
Beta-Carotene (source of vitamin A)	2700 IU	2700 IU
Vitamin B_1 (thiamine mononitrate)	3 mg	3 mg
Vitamin B_2 (riboflavin)	3.4 mg	3.4 mg
Niacinamide	20 mg	20 mg
Pantothenic Acid (calcium pantothenate)	5 mg	5 mg
Vitamin B_6 (pyridoxine HCl)	10 mg	10 mg
Vitamin C (ascorbic acid)	120 mg	120 mg
Vitamin E (dl-alpha tocopheryl acetate)	30 IU	30 IU
Copper (cupric oxide)	2 mg	2 mg
Iodine (potassium iodide)	0.15 mg	0.15 mg
Iron (ferrous fumarate)*	35 mg	35 mg
Magnesium (magnesium oxide)	50 mg	50 mg
Zinc (zinc oxide)	15 mg	15 mg

* Elemental amount

Each oval shaped, blue/dark blue (p.m.), film coated, immediate release tablet contains:

	PregVit®	**PregVit folic 5®**
Folic Acid	1.1 mg	5.0 mg
Vitamin B_{12} (cyanocobalamin)	12 µg	12 µg
Vitamin D_3 (cholecalciferol)	250 IU	250 IU
Calcium (calcium carbonate)*	300 mg	300 mg

* Elemental amount

Nonmedicinal Ingredients (organized alphabetically):

PregVit® *pink (a.m.) tablet contains:*
ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C Red #27, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, starch (corn starch), talc, titanium dioxide.

PregVit® *blue (p.m.) tablet contains:*
ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C Red #27, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, talc, titanium dioxide.

PregVit folic 5® *pink (a.m.) tablet contains:*
ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C Red #27, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, starch (corn starch), talc, titanium dioxide.

PregVit folic 5® ***dark blue (p.m.) tablet contains:***
ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C Red #27, FD&C Blue #1, FD&C Blue #2, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, talc, titanium dioxide.

These products do not contain lactose, gliadin-gluten or tartrazine.

These products are certified Kosher and Halal .

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

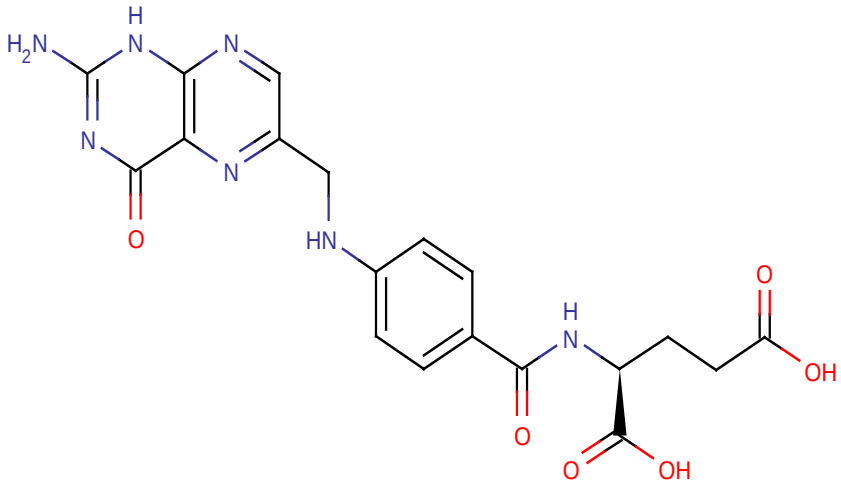
Drug Substance

Proper name: Folic acid

Chemical name: N-[4-[[(2-Amino-1,4-dihydro-4-oxo-6-pteridinyl)-methyl]-amino]benzoyl]- L-glutamic Acid

Molecular formula and molecular mass: $C_{19}H_{19}N_7O_6$ 441.40

Structural formula:



Physicochemical properties: Yellow-orange crystalline powder. Soluble in water. Insoluble in alcohol, ether, acetone.

Other Drug Substances:

Drug Substance	Proper Name	Chemical Name	Molecular Formula and Molecular Mass	Physicochemical Properties
VITAMINS				
Beta-Carotene (source of vitamin A)	Beta Carotene	(all-E)-1,1'-(3,7,12,16-Tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaene-1,18-diyl)bis[2,6,6-trimethylcyclohexene]	$C_{40}H_{56}$ 536.88	Occurs in the pure state as red crystals when re-crystallized from light petroleum. Practically insoluble in ethanol, glycerin and water. Susceptible to oxidation.
Vitamin B_1	Thiamine Mononitrate	Thiazolium, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methyl-, nitrate (salt)	$C_{12}H_{17}N_5O_4S$ 327.36	White to yellow-white crystals. Practically non-hygroscopic. Soluble in water. Slightly soluble in alcohol.
Vitamin B_2	Riboflavin	7,8-dimethyl-10-(D-ribo-2,3,4,5-tetrahydroxypentyl) isoalloxazine	$C_{17}H_{20}N_4O_6$ 376.36	Yellow to orange-yellow, crystalline powder. Soluble in water, alcohol, dilute alkalis.
Niacinamide	Niacinamide	3-Pyridinecarboxamide	$C_6H_6N_2O$ 122.12	White crystalline powder. Soluble in water and alcohol.
Pantothenic Acid	Calcium Pantothenate	β-Alanine, N-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-, calcium slat (2:1), (R)-	$C_{18}H_{32}CaN_2O_{10}$ 476.53	Slightly hygroscopic, white powder. Stable in air. Soluble in water and glycerin. Moderately soluble in alcohol.
Vitamin B_6	Pyridoxine Hydrochloride	3,4-Pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride	$C_8H_{11}NO_3 \cdot HCl$ 205.64	White, crystalline powder. Soluble in water and alcohol. Insoluble in ether.

Drug Substance	Proper Name	Chemical Name	Molecular Formula and Molecular Mass	Physicochemical Properties
Vitamin B_{12}	Cyanocobalamin	5,6-dimethylbenzimidazolyl cyanocobamide	$C_{63}H_{88}CoN_{14}O_{14}P$ 1355.37	Dark red crystals. When exposed to air may absorb water. Soluble in water and alcohol. Insoluble in acetone, chloroform and ether.
Vitamin C	Ascorbic Acid	L-Ascorbic acid	$C_6H_8O_6$ 176.12	White or slightly yellow crystals. Soluble in water, alcohol.
Vitamin D_3	Cholecalciferol	9,10-secocholesta-5,7,10(19)-trien-3-ol, (3β, 5Z, 7E)-	$C_{27}H_{44}O$ 384.64	White crystals. Insoluble in water. Soluble in alcohol, chloroform, and fatty oils. Oxidized and inactivated by moist air within a few days.
Vitamin E	dl-α - Tocopheryl Acetate	2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)-, acetate, (2R)-rel-	$C_{31}H_{52}O_3$ 472.75	Colorless to yellow or green-yellow, clear, viscous oil. Unstable in the presence of alkalis. Insoluble in water. Soluble in alcohol. Miscible with acetone and oils.
MINERALS				
Calcium	Calcium Carbonate	Carbonic acid calcium salt (1:1)	$CaCO_3$ 100.09	White powder or crystals. Insoluble in water and alcohol. Soluble in dilute acids.

Drug Substance	Proper Name	Chemical Name	Molecular Formula and Molecular Mass	Physicochemical Properties
Copper	Cupric Oxide	Copper oxide	CuO 79.55	Steel-grey to black. Slightly soluble in alkalis, soluble in acids and ammonia. Insoluble in water.
Iodine	Potassium Iodide	Potassium iodide	KI 166.00	Colorless or white, cubical crystals, white granules or powder. Becomes yellow in moist air. Soluble in water and alcohol.
Iron	Ferrous Fumarate	2-Butenedioic acid, (E)-, iron(2+)salt	$C_4H_2FeO_4$ 169.9	Red-orange to red-brown powder. It is soluble in water and alcohol.
Magnesium	Magnesium Oxide	Magnesium oxide	MgO 40.30	White, bulky, odorless powder. Practically insoluble in water. Soluble in dilute acids. Insoluble in alcohol.
Zinc	Zinc Oxide	Zinc oxide	ZnO 81.39	White or yellowish powder. Insoluble in water and alcohol. Soluble in dilute acetic or mineral acids, ammonia, ammonium carbonate, fixed alkali hydroxide solutions.

CLINICAL TRIALS

Studies indicate that periconceptional use of supplements containing folic acid may substantially reduce the risk of occurrence (first affected pregnancy) and recurrence (additional affected pregnancies) of neural tube defects (NTDs).

The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommend that women who could become pregnant be advised to take a multivitamin containing 0.4 mg to 1.0 mg of folic acid daily and that women in intermediate- to high-risk categories for NTDs (NTD-affected previous pregnancy, family history, insulin dependent diabetes, epilepsy treatment with carbamazepine, phenobarbital, phenytoin, primidone or valproic acid) be advised that high-dose folic acid (4.0 mg–5.0 mg daily) supplementation is recommended.[30]

Efficacy and safety of PregVit® and PregVit folic 5® formulations are supported by a large body of published literature addressing prenatal multivitamin-mineral supplementation in general and folic acid supplementation specifically.

A tolerability and compliance study was conducted with PregVit® versus a supplement with high iron content, in pregnant women. [20] This randomized, crossover open labelled study was conducted in 138 pregnant women attending outpatient obstetric clinics in Ontario and Quebec. An equal number of women suffering from nausea and vomiting of pregnancy (NVP) and pregnant women without NVP were randomized to receive either PregVit® or a supplement with high iron content for one month. The women were instructed to keep a diary and record any adverse events, severity of their NVP, changes in their diet, use of medications and adherence to the study drug. One month later, the women were given the alternative product and asked to record the same information in the diary for the following month. The primary end point of interest was the mean rate of adverse events including decreased compliance.

A total of 138 patients completed the study and were included in the data analysis. There was a significantly higher incidence of reported constipation (34.8% for the supplement with high iron content versus 22.5% for PregVit®, p=0.03) and significantly longer duration of constipation (4.7% for the supplement with high iron content versus 3.1% for PregVit®, p=0.05) when taking a supplement with high iron content versus PregVit®. This suggests that pregnant women may experience less constipation when taking PregVit®. These results are attributed to the lower iron dose contained in PregVit® versus the supplement with a high iron content (35 mg versus 60 mg). Both products demonstrated similar compliance rates. However, it was found that non-compliance with the supplement with high iron content was related to the severity of nausea and vomiting of pregnancy. This may be explained by a substantially larger tablet size as compared to PregVit® and a direct effect of the higher iron content. Therefore, PregVit® may confer an advantage to women suffering from NVP due to higher tolerability as a result of lower iron content and smaller tablet size.

Additional data regarding the effect of folate and the associated risk reduction have been derived from studies in literature. These studies are presented below in Table 7.

Table 7- Summary of data from literature studies

Study Reference/ Citation	Study Objective	Design Type & Size	Result & Conclusion
Wald et al., 2001	To specify the dose-response relationship between folic acid intake and risk of NTD according to background blood folate concentrations.	Review: 14 studies Dosage & Duration: Up to 1 mg /day between 3 and 24 weeks.	Result: For every 0.1 mg/day rise in folic acid, serum folate increased by about 1 ng/mL in women of childbearing age compared with 2.5 ng/mL in the older group ($p<0.0001$). Conclusion: A rise in serum folate associated with an increase in intake of folic acid over the range of doses is considered additive, while the relationship between the change in serum folate and change in NTD risk is proportional.
Study Reference/	Study Objective	Design Type	Result Conclusion
Wald et al., 2004	To specify the dose-response relation between extra folic acid and the reduction in the risk of NTDs.	Analysis of two studies: Wald et al. (2001) and Medical Research Council (MRC) study.	Result: A 0.2 mg/day folic acid would reduce the risk of NTDs by about 23%, a 0.4 mg folic acid daily intake would reduce the risk by 36%, 1.0 mg per day would reduce the risk by about 57% and the risk of NTDs could be reduced by 85% by taking 5 mg of folic acid daily. Conclusion: A public health policy should be implemented with mandatory fortification of flour and recommend that all women planning a pregnancy take 5 mg of folic acid per day before pregnancy and during the first trimester.

DETAILED PHARMACOLOGY

Pharmacokinetics:

A study using PregVit® was conducted to compare iron absorption of a regular prenatal multivitamin supplement containing both calcium (250 mg) and iron (60 mg) to that of another multivitamin (PregVit®) containing a lower iron dose (35 mg) without calcium. [9] This was a crossover study conducted with a supplement with high iron content and PregVit® [pink (a.m.) tablet] in 12 healthy non-pregnant women. Blood samples were drawn at baseline and 1, 2, 3, 4, 6 and 8 hours post-dose. The mean group AUC values for serum iron were 79.1 ± 36.0 μM*h for PregVit® and 91.4 ± 50.4 μM*h for the supplement with high iron content ($p=0.37$). Upon standardizing the AUC for dose, the relative absorption over the 8 hour time period for PregVit® was significantly higher (2.3 ± 1.0 μM*h) than the supplement with high iron content (1.5 ± 0.8 μM*h) ($p=0.021$). The absorption of iron from PregVit® (a low-iron-containing supplement

that delivered iron separately from calcium) was similar to that from the supplement with high iron content with almost twice the amount of iron. Hence, iron had a higher relative bioavailability in the PregVit® formulation. This was likely due to exclusion of calcium and manganese from the pink (a.m.) tablet with low iron as well as lower amounts of other inhibitors of iron absorption (zinc) and possible preferential enhancement of iron absorption by ascorbate (vitamin C) in the PregVit® pink (a.m.) tablet formulation which had a substantially higher relative amount of ascorbate (vitamin C) to iron.

A crossover study was conducted in 6 healthy non-pregnant women (18-45 years) to determine whether a circadian rhythm of folate pharmacokinetics exists in humans. This is important particularly in the context of PregVit® with folic acid given in the evening. After a six hour fast, the women were randomized to receive either one PregVit® blue (p.m.) tablet in the morning (8:00 a.m.) or one blue (p.m.) tablet in the evening (6:00 p.m.). Serum folate levels were determined from blood samples that were obtained at the start of the study and 1, 2, 3, 4, 6, 8 and 10 hours after ingestion of the tablet. A standardized meal was given 4 hours after dosing, containing 40 µg of folate. The meal chosen was to minimize the amount of folate given and to exclude any molecules known to inhibit the absorption of folate. The mean AUC values for serum folate after the administration of a PregVit® blue (p.m.) tablet were 334.5 ± 119.6 nM*h for morning and 283.1 ± 64.3 nM*h for evening ($p=0.17$). C_{max} values were 135.3 ± 41.7 nM for morning and 130.3 ± 14.2 nM for evening ($p=0.75$). The T_{max} for morning was 1 ± 0.5 hour and 1 ± 0.4 hour for evening. No circadian variation in folate pharmacokinetics was seen. Folic acid contained in the PregVit® blue (p.m.) tablet was absorbed similarly whether administered in the morning or in the evening.[21]

A study comparing folic acid pharmacokinetics was completed where serum folate levels of single dose PregVit® and PregVit folic 5® were measured pre-dose and up to 10 hours post dose in healthy non-pregnant fertile women between the ages of 18 and 45 years. The mean area under the curve (AUC) of 1.1 mg and 5 mg folic acid were 147.6 ± 52.8 (ng/mL)·hr and 997.5 ± 271.9 (ng/mL)·hr, respectively ($p<0.0002$). An approximate 5-fold difference was detected in the peak concentrations (Cmax) between the 2 groups ($p<0.0005$), alongside a slight difference in the times to peak (Tmax) ($p=0.02$). The estimated steady-state serum folate concentrations produced by 1.1 mg and 5 mg folic acid were 6.2 ± 2.2 ng/mL and 41.6 ± 11.3 ng/mL respectively ($p<0.0002$), prior to its summation with initial (baseline) steady-state levels. Single dose administration between 1.1 mg and 5 mg folic acid demonstrated linear pharmacokinetics, with approximately a 5-fold difference between the 2 doses in serum folate contribution to steady-state levels, under ideal adherence.[32]

The study results are summarized in Table 8 below:

Table 8 - Single dose pharmacokinetic comparison of PregVit folic 5® (5 mg) versus PregVit® (1.1 mg) folic acid ingestion, among non-pregnant women of childbearing age

	5 mg folic acid (n=6)	1.1 mg folic acid (n=6)	p-value (Student's t-test)
Baseline (fasting) serum folate concentration, at time=0 (ng/mL)	11.2 ± 3.9	13.2 ± 4.0	0.41
Area under the curve, AUC [(ng/mL)·hr]	997.5 ± 271.9	147.6 ± 52.8	<0.0002
$C_{max,}$ peak serum folate concentration (ng/mL)	273.3 ± 56.3	59.7 ± 18.4	<0.0005
T_{max}, time to achieve peak concentration (hr)	1.8 ± 0.4	1.2 ± 0.4	0.02
Apparent clearance (mL/min)	91.7 ± 37.2	143.6 ± 66.6	0.13
Estimated steady-state serum folate concentration produced by supplemental folic acid (ng/mL)	41.6 ± 11.3	6.2 ± 2.2	<0.0002
Overall estimated steady-state serum folate concentration¶ (ng/mL)	52.8 ± 12.6	19.3 ± 4.2	<0.0001

Note: Data presented as mean ± standard deviation

¶ Overall estimated steady-state serum folate concentration = baseline concentration + estimated steady-state serum folate concentration produced by supplemental folic acid.

REFERENCES

1. Health Canada. Nutrition for a Healthy Pregnancy - National Guidelines for the Childbearing Years. [Online] 2002 Oct 24 [cited 2007 April 23]; [14 pages]. Available from: http://www.hc-sc.gc.ca/fn-an/nutrition/prenatal/national_guidelines_cp-lignes_directrices_nationales_pc_e.html
2. National Institutes of Health. Optimal calcium intake. NIH consensus statement. [Online]. 1994;Jun 6-8;12(4):1-31 [cited 2007 Aug 24]; [23 pages]. Available from: http://consensus.nih.gov/1994/1994OptimalCalcium097html.htm
3. Campbell NR, Hasinoff BB. Iron supplements: a common cause of drug interactions. Br J Clin Pharmacol 1991;31(3):251-5.
4. Van Allen MI, McCourt C, Lee NS, eds. Preconception health: folic acid for the prevention of neural tube defects. A resource document for health professionals 2002. Ottawa,Ontario: Minister of Public Works and Government Services Canada; 2002.
5. Alstead EM. Inflammatory bowel disease in pregnancy. Postgrad Med J 2002;78:23-6.
6. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 2000 Nov 30; 343(22):1608-14.
7. Oakley GP, Bell KN, Weber MB. Recommendations for accelerating global action to prevent folic acid-preventable birth defects and other folate deficiency diseases: Meeting of experts on preventing folic acid-preventable neural tube defects. Birth Defects Research (Part A) Clin Mol Teratol 2004 Nov; 70(11):835-7.
8. Wald NJ. Folic acid and the prevention of neural tube defects. N. Engl. J. Med 2004 Jan 8; 350(2):101-3.
9. Ahn E, Kapur B., and Koren G. Iron bioavailability in prenatal multivitamin supplements with separated and combined iron and calcium. 2004 Sept;26(9):809-13.
10. Bothwell TH. Overview and mechanism of iron regulation. Nutr Rev 1995 Sep; 53(9):237-45.
11. Rossander-Hulten L, Brune M, Sandstrom B, Lonnerdal B, Hallberg L. Competitive inhibition of iron absorption by manganese and zinc in humans. Am J Clin Nutr 1991 Jul; 54(1):152-6.
12. Metz J, McNeil AR, Levin M. The relationship between serum cobalamin concentration and mean red cell volume at varying concentrations of serum folate. Clin Lab Haematol. 2004 Oct; 26(5):323-5.
13. Health Canada. Nutrition for a Healthy Pregnancy - National Guidelines for the Childbearing Years. [Online]. 2007 July 23 [cited 2007 Aug 24]; [14 pages]. Available from: http://www.hc-sc.gc.ca/fn-an/nutrition/prenatal/national_guidelines-lignes_directrices_nationales-06_e.html
14. De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med. 2007 Jul 12; 357(2):135-42.
15. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 7th ed Philadelphia; Lippincott Williams & Wilkins, 2005; xxv, 682-95.
16. Expert Group on Vitamins and Minerals. Safe Upper Levels for Vitamins and Minerals: Folic Acid [Online]. 2003 May [cited 2007 Aug 21]; [10 pages]. Available from: URL: http://www.food.gov.uk/multimedia/pdfs/vitmin2003.pdf
17. Frykman E, Bystrom M, Jansson U, Edberg A, Hansen T. Side effects of iron supplements in blood donors: superior tolerance of heme iron. J Lab Clin Med 1994 Apr;123(4):561–4.

18. Galloway R, McGuire J. Determinants of compliance with iron supplementation: supplies, side effects, or psychology? Soc Sci Med 1994 Aug; 39(3):381–90.
19. Sifakis S, Pharmakides G. Anemia in pregnancy. Ann N Y Acad Sci 2000; 900:125–36.
20. Ahn E, Pairaudeau N, Pairaudeau N. Jr; Cerat, Y.; Couturier, B.; Fortier, A.; Paradis, E., and Koren, G. A randomized cross over trial of tolerability and compliance of a micronutrient supplement with low iron separated from calcium vs. high iron combined with calcium in pregnant women. BMC Pregnancy Childbirth 2006 Apr 4; 6:10.
21. Ahn, E.; Kapur, B., and Koren, G. Study on circadian variation in folate pharmacokinetics. Can J Clin Pharmacol. 2005 Winter; 12(1):e4-9.
22. Suspected ADRs reported to Duchesnay from 2003 to 2007 for PregVit and PregVit folic 5.
23. Suspected ADRs reported to Duchesnay from 2003 to 2008 for PregVit and PregVit folic 5.
24. Chopra IJ, Baber K. Treatment of primary hypothyroidism during pregnancy: is there an increase in thyroxine dose requirement in pregnancy? Metabolism 2003 Jan; 52(1): 122-8.
25. National Academy of Sciences, Institute of Medicine, Food and Nutrition Board, Committee on Nutritional Status During Pregnancy and Lactation, Subcommittee on Dietary Intake and Nutrient Supplements During Pregnancy, Subcommittee on Nutritional Status and Weight Gain During Pregnancy. Nutrition during pregnancy. Part I - Weight gain. Part II - Nutrient supplements. Washington, DC: National Academy Press; 1990.p. 1-23.
26. Medline Plus. Folate (folic acid) [Online] 2006 August 01; [cited 2007 July 7]; [9 pages]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-folate.html
27. Medline Plus. Iron [Online] 2006 August 01; [cited 2007 July 7]; [8 pages]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-iron.html
28. Medline Plus. Tetracycline [Online] 2005 Oct 01; [cited 2007 July 7]; [3 pages]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682098.html
29. Koren G. The way women perceive teratogenic risk. Can J Clin Pharmacol Vol 14(1) Winter 2007:e10-e16; January 5, 2007.
30. Wilson RD, Davies G, Désilets V, Reid GJ, Summers A, Wyatt P et al. SOGC Clinical Practice Guidelines: The Use of Folic Acid for the Prevention of Neural Tube Defects and Other Congenital Anomalies. J Obstet Gynaecol Can. 2003 Nov; 25(11):959-73.
31. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. Lancet 2001; 358: 2069-73.
32. Nguyen P, Boskovic R, Yazdani P, Kapur B, Vandenberghe H, et al. Comparing Folic Acid Pharmacokinetics Among Women of Childbearing Age: Single Dose Ingestion of 1.1 mg Versus 5 mg Folic Acid. Can J Clin Pharmacol. 2008 Aug; 15 (2): e314-e322.

PART III: CONSUMER INFORMATION

Vitamin-Mineral Supplement Tablets
for Prenatal and Postpartum Use

This leaflet is part III of a three-part Product Monograph document designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PregVit®. Contact your doctor, pharmacist or healthcare professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

PregVit® is a vitamin-mineral supplement specially formulated for use in women at least 2-3 months prior to conception, throughout pregnancy and during the postnatal period. Taking PregVit® does not eliminate the need for a balanced nutrition.

What it does:

PregVit® provides a supplement of vitamins and minerals.

There is strong evidence that preventative treatment with folic acid, prior to and during pregnancy, can reduce the risk of fetal neural tube defects (NTDs). NTDs result from improper development and closure of the neural tube during the third and fourth week of development. Pregnancies affected by a NTD may result in a miscarriage or stillbirth, and children born with a NTD may have mild to severe disability or die in early childhood.

Although the use of a folic acid supplement from before conception to early pregnancy reduces the number of NTDs, they can not be completely avoided through folate supplementation because of their various origins. For women who had a prior history of an NTD pregnancy, the recurrence rate of another NTD pregnancy is 2-3%.

There is evidence that increasing the diet with an additional 0.4 mg/day of folic acid would reduce the risk of neural tube defects for all women planning a pregnancy by about 36%, 1 mg per day would reduce the risk by about 57% and the use of 1.1 mg daily would reduce the risk by about 59%.

When it should not be used:

You should not take PregVit® if you are allergic to any of the ingredients of PregVit® or component of the container (see list of medicinal and nonmedicinal ingredients below this section).

What the medicinal ingredients are:

Each oval shaped, pink (a.m.), film-coated, immediate release tablet contains:

Beta-Carotene (source of vitamin A)	2700 IU
Vitamin B_1 (thiamine mononitrate)	3 mg
Vitamin B_2 (riboflavin)	3.4 mg
Niacinamide	20 mg
Pantothenic Acid (calcium pantothenate)	5 mg
Vitamin B_6 (pyridoxine HCl)	10 mg
Vitamin C (ascorbic acid)	120 mg
Vitamin E (dl-alpha tocopheryl acetate)	30 IU
Copper (cupric oxide)	2 mg
Iodine (potassium iodide)	0.15 mg
Iron (ferrous fumarate)*	35 mg
Magnesium (magnesium oxide)	50 mg
Zinc (zinc oxide)	15 mg

* Elemental amount

Each oval shaped, blue (p.m.), film coated, immediate release tablet contains:

Folic Acid	1.1 mg
Vitamin B_{12} (cyanocobalamin)	12 µg
Vitamin D_3 (cholecalciferol)	250 IU
Calcium (calcium carbonate)*	300 mg

* Elemental amount

What the important nonmedicinal ingredients are:

PregVit® *pink (a.m.) tablet contains:*

ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C Red #27, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, starch (corn starch), talc, titanium dioxide.

PregVit® *blue (p.m.) tablet contains:*

ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C Red #27, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, talc, titanium dioxide.

This product does not contain lactose, gliadin-gluten or tartrazine.

This product is certified Kosher and Halal .

What dosage forms it comes in:

PregVit® is supplied in a 30-day blister pack containing 30 oval, pink (a.m.) tablets and 30 oval, blue (p.m.) tablets. Each tablet is imprinted with a pink image of a pregnant woman.

WARNINGS AND PRECAUTIONS

BEFORE you use PregVit® talk to your doctor or healthcare professional if:

- You have a vitamin B_{12} deficiency. Folic acid should be taken with vitamin B_{12} in order to avoid potential problems of the nervous system. Any dose of folic acid over 1 mg per day may require monitoring for vitamin B_{12} by a doctor or healthcare professional.
- You have seizure disorders controlled on anticonvulsant medications (e.g. carbamazepine, phenobarbital, phenytoin, primidone, valproic acid). You may have an increase in seizures when folic acid is taken.

Keep this product out of the reach of children. Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Each PregVit® pink (a.m.) tablet contains 35 mg of elemental iron. No iron is contained in the PregVit® blue (p.m.) tablet

INTERACTIONS WITH THIS MEDICATION

As with most medications, interaction with other drugs is possible.

Tell your doctor, pharmacist or healthcare professional if you are taking any other medications, including prescription, non-prescription or natural health products, or vitamin-mineral supplements.

In particular, the drugs that may interact with PregVit® include:

- Thyroid hormone medications. Absorption of thyroid medications could be reduced if taken at the same time as iron or calcium supplements. Thyroid medications should be taken four hours before or after the pink (a.m.) and the blue (p.m.) tablets of PregVit®.
- Dihydrofolate reductase inhibitors. Dihydrofolate reductase inhibitors (including sulphasalazine, trimethoprim, triamterene) inhibit the absorption and metabolism of folic acid.
- Antiepileptic drugs. Antiepileptic drugs reduce folic acid absorption. Folic acid supplements have worsened seizure control in some people with epilepsy.

PROPER USE OF THIS MEDICATION

Usual dosage schedule:

Take one pink (a.m.) tablet every morning on an empty stomach, one hour before breakfast, with a glass of water. Do not take any food for one hour after taking the pink (a.m.) tablet to help the iron absorption. If you suffer from nausea and/or vomiting in the morning (morning sickness), take the pink (a.m.) tablet two hours or more after breakfast. Take one blue (p.m.) tablet every evening with a glass of water, within one hour of the evening meal to help calcium absorption.

This product is specifically prescribed for you based on your current state of health. Do not give it to others, even if you think they could benefit from taking it, and you yourself must not use it for any other condition than the one for which it was prescribed.

Tablets are not intended to be crushed or split. If you have difficulty swallowing tablets, let your doctor or healthcare professional know.

Special cases:

- For *women taking calcium rich food for breakfast*, the PregVit® **pink (a.m.)** tablet may be taken two (2) hours or more after breakfast. Following administration of the **pink (a.m.)** tablet a wait of one (1) additional hour is recommended before eating in order to optimize the absorption of iron.
- For *women suffering from nausea and/or vomiting in the morning* where it is difficult to take vitamin-mineral supplements on an empty stomach, the PregVit® **pink (a.m.)** tablet may be taken two (2) hours or more after breakfast. Following administration of the **pink (a.m.)** tablet a wait of one (1) additional hour is recommended before eating in order to optimize the absorption of iron.
- For *women taking levothyroxine hormone in the morning*, it is recommended to take the PregVit® **pink (a.m.)** tablet at least four (4) hours apart to optimize the absorption of *levothyroxine hormone*. For *women taking levothyroxine hormone at bedtime*, it is recommended to take the PregVit® **blue (p.m.)** tablet at least four (4) hours apart to optimize the absorption of *levothyroxine hormone*.

Overdose:

In case of accidental overdose, contact a doctor or a **regional Poison Control Centre** immediately.

Do not exceed the recommended dose.

Missed dose:

When a dose has been missed, it should be taken as soon as possible and one pink (a.m.) and one blue (p.m.) tablet should be taken within a 24-hour period. It is recommended that PregVit® pink (a.m.) and blue (p.m.) tablets be taken at least four (4) hours apart in order to optimize the absorption of nutrients.

The prescribed dosing schedule should then continue as directed by doctor or healthcare professional.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects: The most common adverse reactions associated with vitamin-mineral supplements are gastrointestinal symptoms such as constipation, diarrhea, nausea and gastric irritation.

This is not a complete list of side effects.

For any unexpected effects while taking PregVit®, contact your doctor, pharmacist or healthcare professional.

HOW TO STORE IT

Store at room temperature (15 to 30ºC).

Protect from moisture. Contact with moisture may produce surface discoloration or erosion of the tablet.

Keep in a safe place out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for healthcare professionals can be obtained by contacting the sponsor, Duchesnay Inc. at:
2925 Boul. Industriel
Laval, Quebec, Canada
H7L 3W9
Tel: 1-888-666-0611
Fax: 1-888-588-8508

This leaflet was prepared by Duchesnay Inc.

Last revised: January 7, 2009.

PART III: CONSUMER INFORMATION

Vitamin-Mineral Supplement Tablets
High Dose of Folic Acid for Prenatal Use

This leaflet is part III of a three-part Product Monograph document designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PregVit folic 5®. Contact your doctor, pharmacist or healthcare professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

PregVit folic 5® is for use in women who are planning pregnancy or pregnant and have the following conditions:

- a previous pregnancy affected by a neural tube defect, or
- a family history of neural tube defects,
- diabetes or malabsorption disorders,
- are taking medications used for seizure control or that are known to decrease folate levels,
- a folate deficiency requiring a high dose of folic acid supplement.

PregVit folic 5® should be taken at least 2-3 months prior to conception, continuing up to 10-12 weeks after the last menstrual period, or throughout the pregnancy. Taking PregVit folic 5® does not eliminate the need for a balanced nutrition.

What it does:

PregVit folic 5® provides a supplement of vitamins and minerals and 5 mg of folic acid.

There is strong evidence that preventative treatment with folic acid, prior to and during pregnancy, can reduce the risk of fetal neural tube defects (NTDs). NTDs result from improper development and closure of the neural tube during the third and fourth week of development. Pregnancies affected by a NTD may result in a miscarriage or stillbirth, and children born with a NTD may have mild to severe disability or die in early childhood.

Although the use of a folic acid supplement from before conception to early pregnancy reduces the number of NTDs, they cannot be completely avoided through folate supplementation because of their various origins. For women who had prior history of an NTD pregnancy, the recurrence rate of another NTD pregnancy is 2-3%. Consuming 5 mg of folic acid daily has the potential of reducing the incidence of another NTD pregnancy to a recurrence rate of 1%.

There is evidence that increasing the diet with an additional 0.4 mg/day of folic acid would reduce the risk of neural tube defects for all women planning a pregnancy by about 36%, 1 mg per day would reduce the risk by about 57% and the use of a 5 mg tablet daily would reduce the risk by about 85%.

When it should not be used:

You should not be given PregVit folic 5® if you are allergic to any of the ingredients of PregVit folic 5® or component of the container (see list of medicinal and nonmedicinal ingredients below this section).

What the medicinal ingredients are:

Each oval shaped, pink (a.m.), film-coated, immediate release tablet contains:

Beta-Carotene (source of vitamin A)	2700 IU
Vitamin B_1 (thiamine mononitrate)	3 mg
Vitamin B_2 (riboflavin)	3.4 mg
Niacinamide	20 mg
Pantothenic Acid (calcium pantothenate)	5 mg
Vitamin B_6 (pyridoxine HCl)	10 mg
Vitamin C (ascorbic acid)	120 mg
Vitamin E (dl-alpha tocopheryl acetate)	30 IU
Copper (cupric oxide)	2 mg
Iodine (potassium iodide)	0.15 mg
Iron (ferrous fumarate)*	35 mg
Magnesium (magnesium oxide)	50 mg
Zinc (zinc oxide)	15 mg

* Elemental amount

Each oval shaped, dark blue (p.m.), film coated, immediate release tablet contains:

Folic Acid	5 mg
Vitamin B_{12} (cyanocobalamin)	12 µg
Vitamin D_3 (cholecalciferol)	250 IU
Calcium (calcium carbonate)*	300 mg

* Elemental amount

What the important nonmedicinal ingredients are:

PregVit folic 5® ***pink (a.m.) tablet contains:***
ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C Red #27, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, FD&C Yellow #6, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, starch (corn starch), talc, titanium dioxide.

PregVit folic 5® ***dark blue (p.m.) tablet contains:***
ammonium hydroxide, N-butyl alcohol, carnauba wax, D&C red #27, FD&C Blue #1, FD&C Blue #2, isopropyl alcohol, macrogol/PEG 3350, magnesium stearate, polyvinyl alcohol, propylene glycol, shellac glaze, simethicone, sodium croscarmellose, sodium lauryl sulfate, talc, titanium dioxide.

This product does not contain lactose, gliadin-gluten or tartrazine.

This product is certified Kosher and Halal .

What dosage forms it comes in:
PregVit folic 5® is supplied in a 30-day blister pack containing 30 oval, pink (a.m.) tablets and 30 oval, dark blue (p.m.) tablets. Each tablet is imprinted with a pink image of a pregnant woman.

WARNINGS AND PRECAUTIONS

BEFORE you use PregVit folic 5® talk to your doctor or healthcare professional if:

- You have a vitamin B_{12} deficiency. Folic acid should be taken with vitamin B_{12} in order to avoid potential problems of the nervous system. Any dose of folic acid over 1 mg per day may require monitoring for vitamin B_{12} by a doctor or healthcare professional.
- You have seizure disorders controlled on anticonvulsant medications (e.g. carbamazepine, phenobarbital, phenytoin, primidone, valproic acid). You may have an increase in seizures when folic acid is taken.

Keep this product out of the reach of children. Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Each PregVit folic 5® pink (a.m.) tablet contains 35 mg of elemental iron. No iron is contained in the PregVit folic 5® dark blue (p.m.) tablet.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interaction with other drugs is possible.

Tell your doctor, pharmacist or healthcare professional if you are taking any other medications, including prescription, non-prescription or natural health products, or vitamin-mineral supplements.

In particular, these drugs that may interact with PregVit folic 5® include:

- Thyroid hormone medications. Absorption of thyroid medications could be reduced if taken at the same time as iron or calcium supplements. Thyroid medications should be taken four hours before or after the pink (a.m.) and the dark blue (p.m.) tablets of PregVit folic 5®.
- Dihydrofolate reductase inhibitors. Dihydrofolate reductase inhibitors (including sulphasalazine, trimethoprim, triamterene) inhibit the absorption and metabolism of folic acid.
- Antiepileptic drugs. Antiepileptic drugs reduce folic acid absorption. Folic acid supplements have worsened seizure control in some people with epilepsy.

PROPER USE OF THIS MEDICATION

Usual dosage schedule:
Take one pink (a.m.) tablet every morning on an empty stomach, one hour before breakfast, with a glass of water. Do not take any food for one hour after taking the pink (a.m.) tablet to help the iron absorption. If you suffer from nausea and/or vomiting in the morning (morning sickness), take the pink (a.m.) tablet two hours or more after breakfast. Take one dark blue (p.m.) tablet every evening with a glass of water, within one hour of the evening meal to help calcium absorption.

This product is specifically prescribed for you based on your current state of health. Do not give it to others, even if you think they could benefit from taking it, and you yourself must not use it for any other condition than the one for which it was prescribed.

Tablets are not intended to be crushed or split. If you have difficulty swallowing tablets, let your doctor or healthcare professional know.

Special cases:

- For *women taking calcium rich food for breakfast*, the PregVit folic 5® **pink (a.m.)** tablet may be taken two (2) hours or more after breakfast. Following administration of the **pink (a.m.)** tablet a wait of one (1) additional hour is recommended before eating in order to optimize the absorption of iron.
- For *women suffering from nausea and/or vomiting in the morning* where it is difficult to take vitamin-mineral supplements on an empty stomach, the PregVit folic 5® **pink (a.m.)** tablet may be taken two (2) hours or more after breakfast. Following administration of the **pink (a.m.)** tablet a wait of one (1) additional hour is recommended before eating in order to optimize the absorption of iron.
- For *women taking levothyroxine hormone in the morning*, it is recommended to take the PregVit folic 5® **pink (a.m.)** tablet at least four (4) hours apart to optimize the absorption of *levothyroxine hormone*. For *women taking levothyroxine hormone at bedtime*, it is recommended to take the PregVit folic 5® **dark blue (p.m.)** tablet at least four (4) hours apart to optimize the absorption of *levothyroxine hormone*.

Overdose:
In case of accidental overdose, contact a doctor or **regional Poison Control Centre** immediately.

Do not exceed the recommended dose.

Missed dose:
When a dose has been missed, it should be taken as soon as possible and one pink (a.m.) and one dark blue (p.m.) tablet should be taken within a 24-hour period. It is recommended that PregVit folic 5® pink (a.m.) and dark blue (p.m.) tablets be taken at least four (4) hours apart in order to optimize the absorption of nutrients.
The prescribed dosing schedule should then continue as directed by doctor or healthcare professional.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects: The most common adverse reactions associated with vitamin-mineral supplements are gastrointestinal symptoms such as constipation, diarrhea, nausea and gastric irritation.

This is not a complete list of side effects.

For any unexpected effects while taking PregVit folic 5®, contact your doctor, pharmacist or healthcare professional.

HOW TO STORE IT

Store at room temperature (15 to 30ºC).

Protect from moisture. Contact with moisture may produce surface discoloration or erosion of the tablet.

Keep in a safe place out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for healthcare professionals can be obtained by contacting the sponsor, Duchesnay Inc. at:
2925 Boul. Industriel
Laval, Quebec, Canada
H7L 3W9
Tel: 1-888-666-0611
Fax: 1-888-588-8508

This leaflet was prepared by Duchesnay Inc.

Last revised: January 7, 2009.