# Folic acid
## Newborn use only

**2019**

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| **Alert** | There is no folic acid in Penta-vite and Brauer Baby & Toddler Liquid Multivitamin, two commonly used multivitamin preparations in New South Wales.<br>Human milk fortifiers contain folate and provide 44-64 microgram/kg/day of folate at 150 mL/kg/day of fortified human milk. |
| **Indication** | 1. Prevention and treatment of folic acid deficiency including megaloblastic anaemia.<br>2. Nutritional treatment of anaemia when folic acid intake may be inadequate.<br>3. Supplementation following severe haemolysis – unclear evidence. |
| **Action** | Folate (Vitamin B9) is necessary for the synthesis of purines and thymine required for DNA formation. It is necessary for red cell maturation and promotion of cellular growth. The active form of folate is tetrahydrofolate [1, 2]. Supplemental folate is more bioavailable than folate normally present in food (85% versus 50%).<br>Folinic acid is a metabolically active reduced form of folate that bypasses dihydrofolate reductase. Folate and folinic acid have a protective and probably similar effect against methotrexate related adverse effects in patients with inflammatory disease [3, 4]. As folinic acid is expensive, folate may be preferred. |
| **Drug Type** | Vitamin B9 |
| **Trade Name** | Blackmores Folate Tablets; Foltabs Tablets; Megafol Tablets; Folic Acid Oral Solution; Folic Acid Injection Biological Therapies; Folic Acid Injection Phebra |
| **Presentation** | 5 mg/mL 1 mL vial [Phebra] (each vial contains 34.5 mg/mL of sodium)<br>15 mg/mL 1 mL vial [Biological Therapies] (each vial contains 2.4 mg/mL of sodium)<br>0.05mg/mL (50microgram/mL) or 1 mg/mL oral solution can be prepared by pharmacy.<br>500 microgram Megafol tablet, 5mg Megafol tablet |
| **Dosage/Interval** | Enteral supplementation for very low birthweight infants*<br>50 micrograms/kg/day (Recommended Daily Intake: 35-100 micrograms/kg/day)[11]<br><br>Treatment of folic acid deficiency:<br>100 microgram/day (<u>not</u> per kg)<br><br>*Estimated enteral intakes based on 100 mL/kg human milk and 150 mL/kg fortified human milk are 8.5-16 and 44-64 microgram/kg/day respectively.[10] |
| **Route** | Oral |
| **Maximum Daily Dose** | |
| **Preparation/Dilution** | **Option 1 (using the vials for injection)**<br>In-house pharmacy can prepare an oral solution using the vials for injection as follows:<br>**Note: pH of solution needs be adjusted to 8-8.5 using sodium hydroxide. This can be done by adding WFI to approximately 90% of final volume, measure pH, adjust pH if necessary, then make to final volume.**<br>1mg/mL oral solution:<br>Add 30 mg of folic acid to water for injection to make a final volume of 30 mL giving final concentration of 1 mg/mL.<br>0.05mg/mL (50microgram/mL) oral solution:<br>Add 5 mg of folic acid to water for injection to make a final volume of 100 mL giving final concentration of 0.05mg/mL (50microgram/mL).<br><br>**Option 2 (using tablets or powder)**<br>In-house pharmacy can prepare a Syrspend SF PH4 formula using folic acid tablets or powder to prepare a 1mg/mL oral suspension:<br><br>Add 30mg of folic acid powder to Syrspend SF PH4 to make a final volume of 30 mL giving final concentration of 1 mg/mL suspension. |
| **Administration** | PO: Administer orally with or without feeds |
| **Monitoring** | No specific monitoring required. |

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| **Contraindications** | No information. |
| **Precautions** | No information. |
| **Drug Interactions** | Phenytoin: Concurrent use of folic acid and phenytoin may result in decreased folate concentrations and decreased phenytoin effectiveness.<br>Phenobarbital (phenobarbitone): Folic acid may decrease phenobarbital (phenobarbitone) concentration and its therapeutic effect; monitor phenobarbital (phenobarbitone) concentration and clinical effect. |
| **Adverse Reactions** | Toxicity from over dosage is not reported in newborns. In preterm infants, high folate concentrations have been associated with low zinc [5]. Weight loss, neurological, gastrointestinal and psychological symptoms were also reported in adults on high doses [6]. |
| **Compatibility** | Not applicable. |
| **Incompatibility** | Not applicable. |
| **Stability** | The compounded option using injections is stable for 30 days and the Syrspend PH4 formula is stable for 90 days. Refrigerate. Protect from light. |
| **Storage** | Refrigerate (2–8°C) oral solution prepared in-house.<br>Tablets store below 25°C. |
| **Special Comments** | |
| **Evidence summary** | **Folate deficiency**<br>Folate deficiency results in growth retardation, anaemia, abnormalities in neurologic status and small intestinal morphology [7]. The haematological manifestations of folate deficiency include hypersegmentation of neutrophils, megaloblastosis and anaemia. Serum folate levels reflect recent dietary intake, whereas red cell folate reflects longer term status [8].<br><br>**Folate Intakes**<br>Hay et al reported the folate status in a cohort of Norwegian term breastfed infants. Folate levels remained adequate to 6 months age up until complementary feeds were introduced [9]. The amount of folic acid present in human milk (8.8 to 16 micrograms per 100 mL) may not be enough to meet the recommended intakes for preterm infants [10]. The use of human breast milk fortifiers or preterm formulas with higher folic acid content has been recommended for preterm infants [11].<br>The average folate intake from parenteral nutrition is 40 microgram/kg/day. The average concentration in feeds is: fortified human milk 30 to 40 microgram/100 mL and preterm formula 35 microgram/100 mL).<br>Oncel et al [12] reported preterm infants receiving parenteral nutrition with high folic acid content (100 microgram/100 mL) had no risk of folate deficiency up to 2 months of age. Preterm infants on fortified human milk or preterm formula also maintained serum folate concentrations. However, preterm infants fed from birth with unfortified human milk had low folate intakes, especially when mothers were smokers and/or did not receive folic acid supplementation during pregnancy. However, this study, and another by Spotswood et al, reported preterm neonates did not develop folate deficiency up to 37 weeks postmenstrual age or discharge [12, 13].<br><br>The ESPGHAN recommended intake of folic acid for preterm infants is 35 to 100 microgram/kg/day (32 to 90 microgram/100 kCal) [11]. [LOE II-III GOR C]<br><br>**Efficacy**<br>***Prevention of anaemia:*** A systematic review of folate supplementation on folate status and health outcomes in infants, children and adolescents reported there is no evidence that additional intake of folate influences haemoglobin levels in non-anaemic paediatric patients [8]. In addition, there was insufficient evidence to determine an effect on growth. [LOE II-III; GOR C]<br>***Treatment of megaloblastic anaemia:*** A case series documented response to folate 60 to 480 micrograms/ day intramuscularly in folate deficient infants with megaloblastic anaemia [14]. [LOE IV GOR C] |

***Preterm or low birth weight infants:*** A systematic review of folate supplementation on folate status and health outcomes in infants, children and adolescents reported limited data suggest that supplementing the diet of low-birth-weight infants with folic acid may moderate the rapid fall of serum folate and red cell folate in the first months of life [8]. In a RCT in 141 low-birthweight infants, folic acid doses of 25, 50, and 75 micrograms/day were reported to be adequate and affect serum folate levels similarly [15]. There was no significant difference in rehospitalisation rates for transfusion although the study is underpowered. Another RCT in 184 infants born <1800 g and <36 weeks gestation compared oral 100 micrograms folate/day for 4 months versus 100 micrograms vitamin B-12 intramuscularly monthly for 4 months versus both supplements or neither supplement in infants treated with iron and vitamin E [16]. Folate supplementation significantly decreased the decline in haemoglobin compared to the unsupplemented group, although the smallest decline in haemoglobin was reported in infants who received B12 alone or in combination with folate. Transfusion requirements were not reported.

**Recommendation:** The current ESPGHAN recommended enteral folic acid intake for preterm infants is 35 to 100 microgram/kg/day [11]. The recent ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Vitamins recommend routine supplementation of folic acid to prevent development of folic acid deficiency in preterm infants [17]. Erythropoietin therapy for prevention and treatment of anaemia of prematurity may increase folic acid deficiency. Therefore, ESPGHAN has recommended combined therapy of B12 and folic acid to enhance erythropoiesis. According to the ESPGHAN 2005 Guidelines, the current recommended dose of FA in PN is 56 microgram/kg/day for infants and 140 mg/day for children. When needed as a treatment to improve erythropoiesis, the recommended dose is 35 to 100 microgram/kg/day. [LOE II-III GOR C]

**Treatment of other anaemias:**

***Rhesus haemolytic disease of the newborn:*** Two reviews [18, 19] of the management of rhesus haemolytic disease reported that although administration of folic acid until 3 months of age might hypothetically decrease the need for top-up transfusions of red blood cells, current studies do not provide any evidence that administration of folic acid to infants with haemolytic disease affects the haemoglobin level [18] or reduces the need for top-up transfusions of red blood cells [18, 19]. Folic acid dosages reported in the literature vary from 25 micrograms to 5 mg/d and side effects (such as rash, fever) were uncommon. A routine supplement of folate 50 micrograms was suggested for infants with haemolytic disease of the newborn during the first three months of life [19].

***Sickle cell anaemia:*** A systematic review found a single trial of folate 5 mg daily versus placebo in 117 children with sickle cell disease aged 6 months to 4 years and reported increased in serum folate levels but no effect on haemoglobin or symptoms of sickle cell disease [20]. [LOE II GOR C/D]

***Hereditary spherocytosis (HS):*** Megaloblastic anaemia has been reported in patients with HS. The General Haematology Task Force of the British Committee for Standards in Haematology recommend folate (2.5 mg/day up to 5 years age, and 5 mg/day thereafter) in severe and moderate HS, but is probably not necessary in mild HS [21]. [LOE III/IV, GOR C]

**Concurrent therapy with dihydrofolate reductase inhibitors (trimethoprim/sulfamethoxazole; Pyrimethamine / sulfadiazine; methotrexate):**

***Methotrexate:*** Folate and folinic acid have a protective and probably similar effect against methotrexate related adverse effects (including a reduction in gastrointestinal side effects, hepatic dysfunction and discontinuation of MTX treatment for any reason) in patients with inflammatory disease [3, 4]. As folinic acid is expensive, folate may be preferred.

***Pyrimethamine / sulfadiazine:*** Current guidelines for treatment of the infant with congenital toxoplasmosis are for use of pyrimethamine and sulfadiazine plus folinic acid [22,23]. Folinic acid 10 mg three-times a week is recommended until 1 week following cessation of Pyrimethamine treatment. It was advised not to use folic acid as a substitute for folinic acid [24]. Levels of folinic acid in the CSF from folinic acid supplemented infants treated with

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| | pyrimethamine for congenital toxoplasmosis are thought to be too low to inhibit the effect of pyrimethamine [25]. However, there are no clinical trials comparing folate or folinic acid versus placebo in infants with toxoplasmosis.<br>***Trimethoprim/sulfamethoxazole:*** There are no clinical trials comparing folate or folinic acid versus placebo in infants with treated with trimethoprim/sulfamethoxazole.<br>**Safety**<br>Folic acid toxicity is not reported in newborns [17]. However, higher, so-called pharmacological doses may mask neurological manifestations of pernicious anaemia and may reduce the efficacy of anticonvulsant medications [17]. High folate concentrations were associated with low zinc concentrations in preterm infants [5]. Weight loss, neurological, gastrointestinal and psychological symptoms were reported in adults on high doses [6]. |
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