Alert	Routine folic acid supplementation is not required in preterm infants on fully fortified human milk. There is no folic acid in Penta-vite Liquid Multivitamins (with Iron and for Infants), two commonly used multivitamin preparations in New South Wales.
Indication	Prevention and treatment of folic acid deficiency. Moderate to severe hereditary spherocytosis.
Action	Folic acid is essential for formation of coenzymes that participate in nucleic acid synthesis (particularly purines and pyrimidines), the metabolism of some amino acids and the catabolism of histidine. Folic acid is required for maintenance of erythropoiesis. It is used as a supplement before and during pregnancy to prevent neural tube defects.
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	Auspman 500 microg (0.5 mg)/mL oral solution (contains 10.55% v/v ethanol; 10.55 mL ethanol in 100 mL)) 5 mg/mL 1 mL vial [Phebra] (each vial contains 34.5 mg/mL of sodium) 15 mg/mL 1 mL vial [Biological Therapies] (each vial contains 2.4 mg/mL of sodium) 1 mg/mL oral solution can be prepared by pharmacy. 500 microg/tablet
Dosage/Interval	Enteral supplementation* Preterm infants: 35–100 microg/kg/day[2,10] Full term infants (0–6 months) : 65 microg/day (not per kg) Treatment of folic acid deficiency (including moderate to severe hereditary spherocytosis): 100 microg/day (not per kg) *Estimated enteral intakes based on 100 mL/kg human milk and 170 mL/kg fortified human milk are 8.5 and 50-73 microg/kg/day respectively.
Route	Oral
Maximum Daily Dose	
Preparation/Dilution	PO: In-house pharmacy can prepare a 1 mg/mL oral solution using the vials for injection as follows: 1. Use a needle and syringe to withdraw 6 mL (= 30 mg) of folic acid injection from 6 vials [Phebra] or 2 vials [Biological Therapies] and transfer to amber glass bottle. 2. Measure and add 24 mL of sterile water for irrigation to glass bottle and mix thoroughly.
Administration	PO: Administer orally with or without feeds
Monitoring	No specific monitoring required.
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. Increase dose of phenytoin as required. Phenobarbital (phenobarbitone): When given for folic acid deficiency, may decrease phenobarbital (phenobarbitone) concentration and its therapeutic effect; monitor phenobarbital (phenobarbitone) concentration and clinical effect. Increase dose of phenobarbital (phenobarbitone) as required.
Adverse Reactions	Toxicity from overdosage is not reported in newborns. In adults, high folate concentrations have been associated with low zinc (Fuller 1992). Weight loss, neurological, gastrointestinal and psychological symptoms were also reported in adults on high doses (Campbell 1996).
Compatibility	Not applicable.
Incompatibility	Not applicable.
Stability	Oral solution prepared in-house is stable for 60 days. Refrigerate. Protect from light.
Storage	Auspman 500 microg/mL oral solution to be stored below 25°C Refrigerate (2–8°C) oral solution prepared in-house 500 microg tablets store below 25°C

Special Comments	
Evidence summary	**Folate Intakes** Human milk, on average, contains 85 microg/L of folic acid. With the availability of new parenteral nutrition products, fortified human milk and preterm formulas containing folic acid, additional folic acid supplementation in the NICU population has become a source of controversy.[1] In a recent study by Oncel et al,[1] preterm infants receiving parenteral nutrition with high folic acid content (100 microg/100 mL) have no risk of folate deficiency up to 2 months of age; preterm infants on fortified human milk or preterm formula also maintained sufficient serum folate concentrations. However, preterm infants fed orally from birth with unfortified human milk could be at risk for folate deficiency, especially when mothers were smokers and/or did not receive folic acid supplementation during pregnancy. None of the preterm infants in their study developed folate deficiency despite not receiving any added folic acid supplementation. In comparison, average folate concentrations in our NICU feeds: Parenteral nutrition (40 microg/kg/day), fortified human milk (30–40 microg/100 mL) and preterm formula (35 microg/100 mL). Folate deficiency Folate deficiency results in growth retardation, anaemia and abnormalities in neurologic status and small intestinal morphology.[2] Folate deficiency is diagnosed by serum and red cell folate concentrations, urinary FIGLU (formiminoglutamate), MCV and blood film. The haematological manifestations of folate deficiency include hypersegmentation of neutrophils, megaloblastosis and anaemia.[2] Efficacy Two non-random trials in the 1970s with folate supplementation results in mixed results.[4,5] In an RCT by Worthington-White et al,[6] 184 premature infants < 1800 g at birth and < 36 wk gestation, were entered into a study investigating the role of additional folate and vitamin B-12 supplementation on the anaemia of prematurity. Patients were randomly assigned to 4 groups to receive orally 0.1 mg folate/d for 4 mo, 100 microgram vitamin B-12 intramuscularly monthly for 4 mo, both supplements or neither. All other activities including parenteral nutrition were carried out according to established practices, irrespective of study group. By 10–12 wk, infants treated with vitamin B-12 alone or combined with folate had higher haemoglobin values than the untreated ($P < 0.0005$) or solely folate-treated ($P < 0.01$) groups. These findings held true irrespective of wide variations in treatment and feeding practices. Hereditary spherocytosis (HS) Haematology Task Force of the British Committee for Standards in Haematology (BCSH) Guidelines:[12,13] Folic acid replacement is probably only required as a routine for children with severe haemolysis and in pregnancy, whatever the severity of the HS. Consideration should be given to the socio-economic environment of the child and their diet, in addition to the severity of the HS, before committing a child to lifelong medication. The National Diet and Nutrition Survey in the UK showed that at all ages the average daily intake in 1995 was well above the reference nutrient intake, being 143% for children over 4 years, and 184% in children under 4 years, suggesting that folate supplementation is recommended in severe and moderate HS, but is probably not necessary in mild HS. A reasonable daily dose would be 2.5 mg/day up to the age of 5 years, and 5 mg/day thereafter. However no specific dose recommendations are given for neonates or young infants. Safety While toxicity is not reported in newborns, high folateconcentrations in adults has been associated with low zinc.[7] Weight loss, neurological, gastrointestinal and psychological symptoms were also reported in adults on high doses.[8] A Cochrane systematic review is underway to determine the effectiveness of folic acid supplementation in the prevention of anaemia of prematurity.[9]
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Original version Date: 15/11/2016	**Author: Neonatal Medicines Formulary Consensus Group**
Current Version number: 1.0	**Version Date:** 15/11/2016
Risk Rating: Medium	**Due for Review:** 15/11/2019
Approval by:	**Approval Date:**