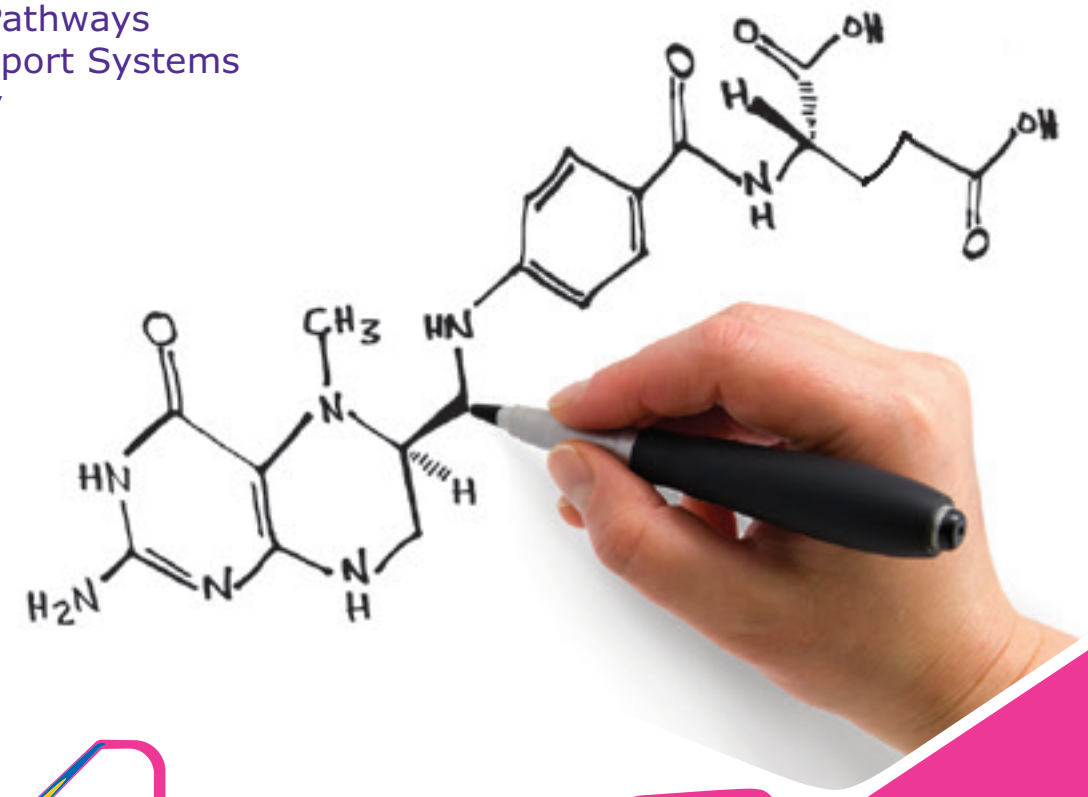
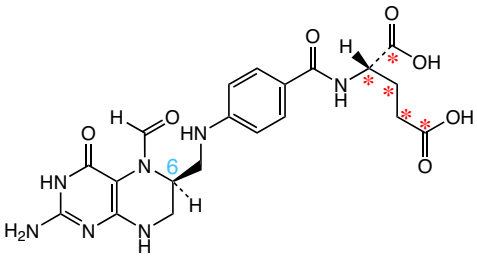
Folate Compounds
From The Leading Folate Chemistry Experts

Folate Substance List
Natural Folates
Biochemical Pathways
Cellular Transport Systems
Folate History



SAFC®
Pharma & Biopharma Raw Material Solutions

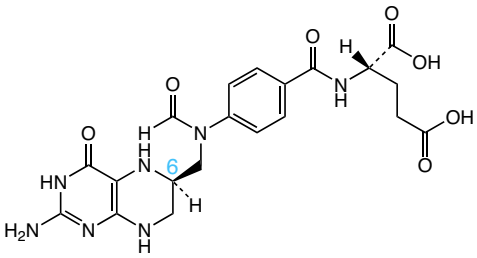
Folate Substance List



5-Formyltetrahydrofolate (Leucovorin)

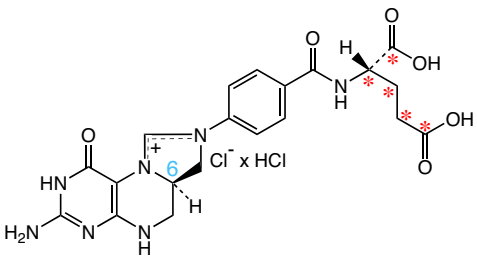
$C_{20}H_{23}N_7O_7$ (6R,S)-, (6R)-, (6S)-5-CHO-H_4PteGlu,
MW 473.44 Ca- or Na_2-salt

$C_{15}{}^{13}C_5H_{23}N_7O_7$ (6S)-5-CHO-H_4Pte[$^{13}C_5$]Glu, Ca-salt
MW 478.44



10-Formyltetrahydrofolate

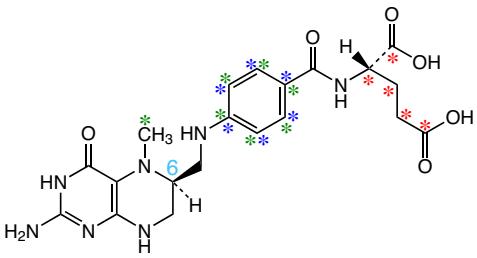
$C_{20}H_{23}N_7O_7$ (6R,S)-, (6S)-, (6R)-10-CHO-H_4PteGlu,
MW 473.44 Ca- or Na_2-salt



5,10-Methenyltetrahydrofolate (Anhydroleucovorin)

$C_{20}H_{23}Cl_2N_7O_6$ (6R,S)-, (6R)-, (6R)-5,10-CH^+-H_4PteGlu-
MW 528.35 Cl x HCl (Cl x HCl salt)

$C_{15}{}^{13}C_5H_{23}Cl_2N_7O_6$ (6R)-5,10-CH^+-H_4Pte[$^{13}C_5$]Glu-
MW 533.35 Cl xHCl



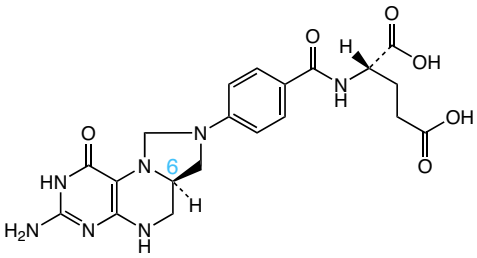
5-Methyltetrahydrofolate

$C_{20}H_{25}N_7O_6$ (6R,S)-, (6R)-, (6S)-5-CH_3-H_4PteGlu,
MW 459.46 Ca- or Na_2-salt

$C_{15}{}^{13}C_5H_{25}N_7O_7$ (6S)-5-CH_3-H_4Pte[$^{13}C_5$]Glu, Ca-salt
MW 464.46

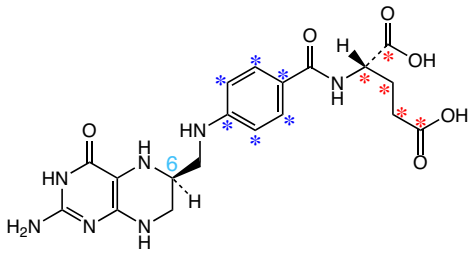
$C_{13}{}^{13}C_6H_{25}N_7O_7$ (6S)-5-CH_3-H_4[$^{13}C_6$]PteGlu, Ca-salt
MW 465.46

$C_{13}{}^{13}C_7H_{25}N_7O_6$ (6S)-5-$^{13}CH_3$-H_4[$^{13}C_6$]PteGlu, Ca-salt
MW 466.46



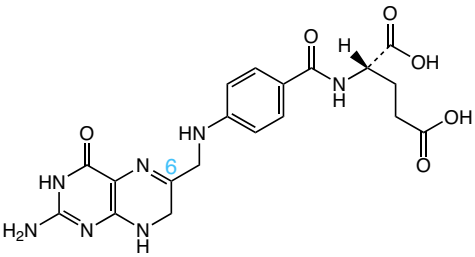
5,10-Methylenetetrahydrofolate

$C_{20}H_{23}N_7O_6$ (6R,S)-, (6S)-, (6R)-5,10-CH_2-H_4PteGlu,
MW 457.44 Ca- or Na_2-salt



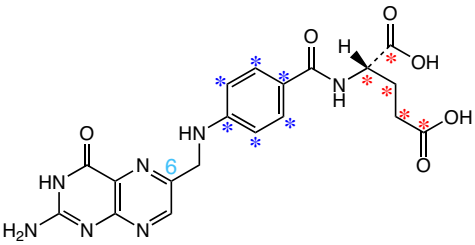
Tetrahydrofolate

$C_{19}H_{23}N_7O_6$ MW 445.43	(6R,S)-, (6R)-, (6S)-H_4PteGlu, Ca- or Na_2-salt
$C_{14}{}^{13}C_5H_{23}N_7O_6$ MW 450.43	(6S)-H_4Pte[$^{13}C_5$]Glu, free acid form
$C_{13}{}^{13}C_6H_{23}N_7O_6$ MW 451.43	(6S)-H_4[$^{13}C_6$]PteGlu, free acid form



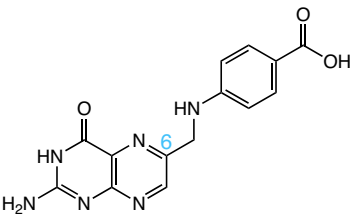
7,8-Dihydrofolate

$C_{19}H_{21}N_7O_6$ MW 443.41	7,8-H_2PteGlu, free acid form



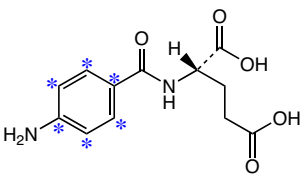
Folic acid (Pteroylglutamic acid)

$C_{19}H_{19}N_7O_6$ MW 441.40	PteGlu, free acid form, Na_2-salt
$C_{14}{}^{13}C_5H_{19}N_7O_6$ MW 446.40	Pte[$^{13}C_5$]Glu, free acid form
$C_{13}{}^{13}C_6H_{19}N_7O_6$ MW 447.40	[$^{13}C_6$]PteGlu, free acid form



Pteroic acid

$C_{14}H_{12}N_6O_3$ MW 312.28	Pte, free acid form

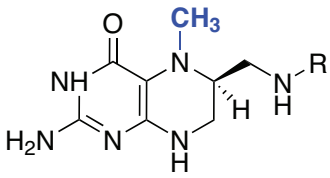


4-Aminobenzoylglutamic acid (PABGA)

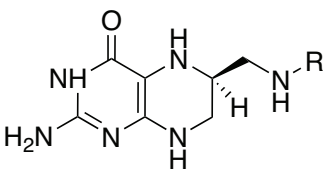
$C_{12}H_{14}N_2O_5$ MW 266.25	7-(4-Aminobenzoyl)-L-glutamic acid, free acid form
$C_6{}^{13}C_6H_{14}N_2O_5$ MW 272.25	7-(4-Amino[$^{13}C_6$]benzoyl)-L-glutamic acid, free acid form

Structure and nomenclature of natural diastereoisomer
*$^{13}C_5$-labeled form available
*$^{13}C_6$-labeled form available
*$^{13}C_7$-labeled form available

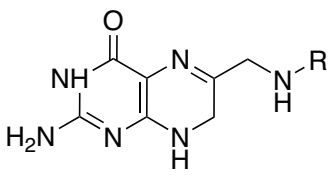
Natural Folates



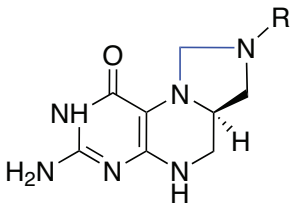
(6S)-**5-Methyl**tetrahydrofolate



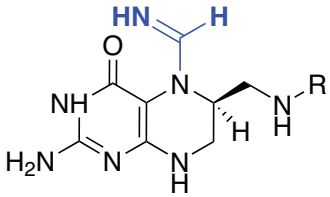
(6S)-Tetrahydrofolate



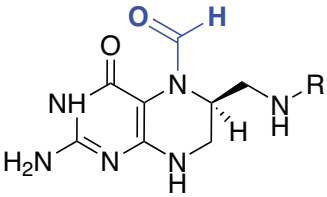
7,8-Dihydrofolate



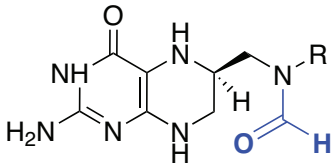
(6R)-**5,10-Methylene**tetrahydrofolate



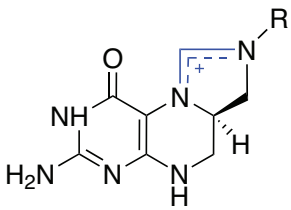
(6S)-**5-Formimino**tetrahydrofolate



(6S)-**5-Formyl**tetrahydrofolate

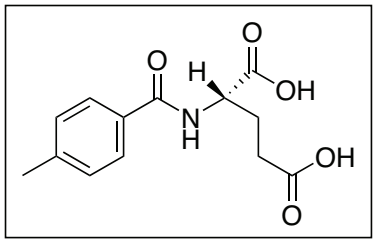


(6R)-**10-Formyl**tetrahydrofolate



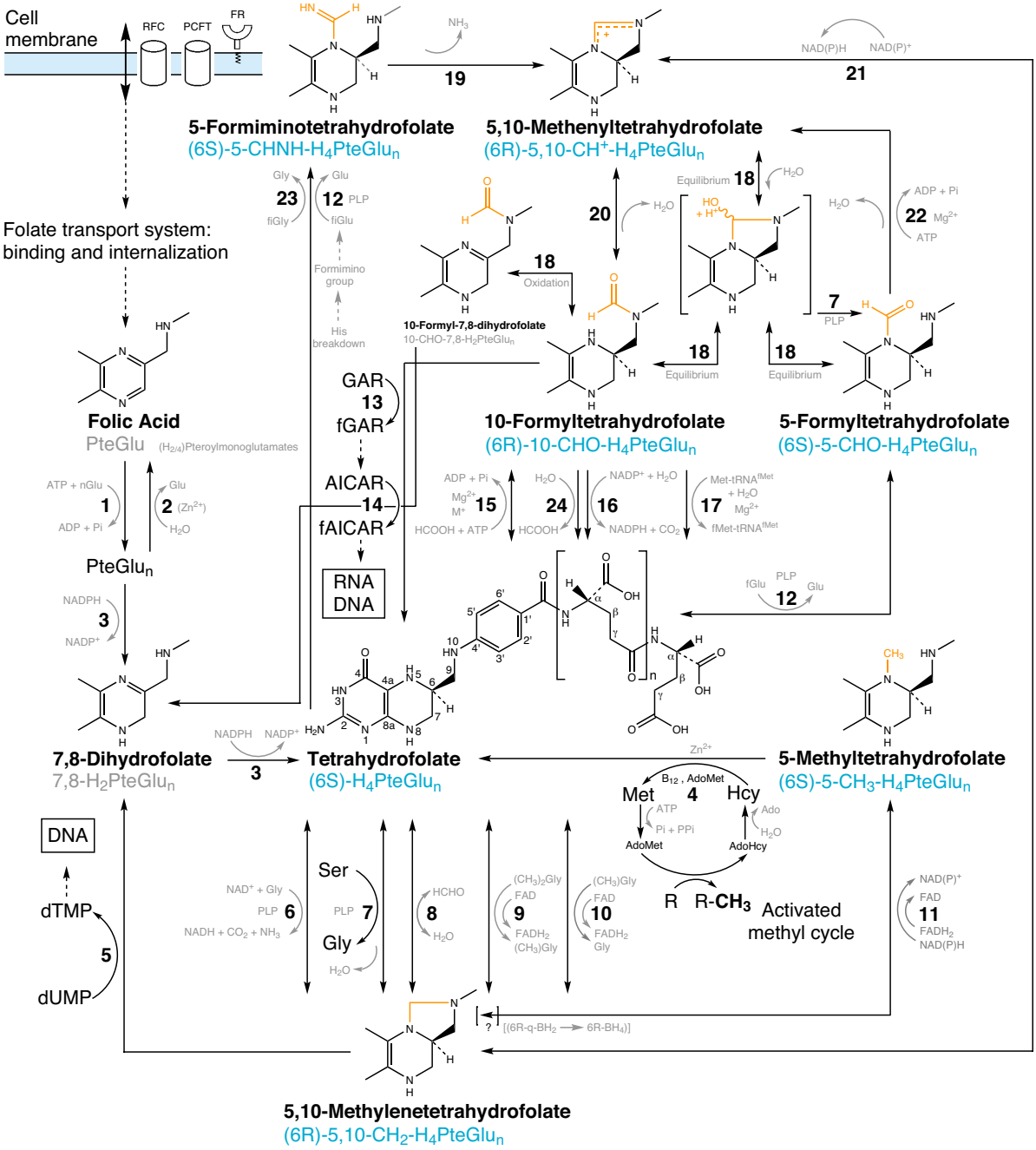
(6R)-**5,10-Methenyl**tetrahydrofolate

R =



benzoyl-*L*-glutamic acid

Biochemical Pathways of Folates



1 Folylpolyglutamate synthase EC 6.3.2.17 (FPGS, FPGS)
2 γ-Glutamyl hydrolase EC 3.4.19.9
3 Dihydrofolate reductase EC 1.5.1.3 (DHFR, DHFR, DHFR2)
4 Methionine synthase EC 2.1.1.13 (MTR)
5 Thymidylate synthase EC 2.1.1.45 (TYMS, TYMS, TYMS)
6 Glycine cleavage system[1] (GLDC/DLD/AMT/GCSH)
7 Serine hydroxymethyltransferase EC 2.1.2.1 (SHMT1, SHMT2α, SHMT1, SHMT2α, SHMT2)
8 Equilibrium (non-enzymatic reaction)
9 Dimethylglycine dehydrogenase EC 1.5.99.2 (DMGD)
10 Sarcosine dehydrogenase EC 1.5.8.3 (SARDH)
11 5,10-Methylenetetrahydrofolate reductase EC 1.5.1.20 (MTHFR)
12 Formimidoyltransferase-cyclodeaminase EC 2.1.2.5[2] (FTCD)
13 Trifunctional purine biosynthetic protein adenosine-3 EC 2.1.2.2 (GART)
14 Bifunctional purine biosynthesis protein PURH EC 2.1.2.3 (ATIC)

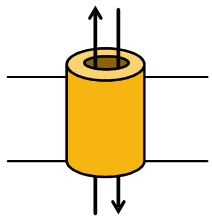
cytosolic
mitochondrial
nuclear

15 C-1-tetrahydrofolate synthase, EC 6.3.4.3[3] (MTHFD1, MTHFD1)
Monofunctional C1-tetrahydrofolate synthase EC 6.3.4.3 (MTHFD1L)
16 10-Formyltetrahydrofolate dehydrogenase EC 1.5.1.6 (ALDH1L1, ALDH1L2)
17 Methionyl-tRNA formyltransferase EC 2.1.2.9 (MTFMT)
18 Non-enzymatic reactions
19 Formimidoyltransferase-cyclodeaminase EC 4.3.1.4[2] (FTCD)
20 C-1-tetrahydrofolate synthase EC 3.5.4.9[3] (MTHFD1, MTHFD1)
Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase EC 3.5.4.9[4] (MTHFD2/MTHFD2L)
21 C-1-tetrahydrofolate synthase EC 1.5.1.5[3] (MTHFD1, MTHFD1)
Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase EC 1.5.1.15[4] (MTHFD2/MTHFD2L)
22 5-Formyltetrahydrofolate cyclo-ligase EC 6.3.3.2 (MTHFS)
23 Glycine formimidoyltransferase EC 2.1.2.4
24 10-Formyltetrahydrofolate deformylase EC 3.5.1.10

1) Glycine cleavage system (EC 1.4.4.2, EC 1.8.1.4, EC 2.1.2.10)
2) Bifunctional enzyme in eukaryotes (EC 2.1.2.5, EC 4.3.1.4)
3) Trifunctional enzyme in eukaryotes (EC 6.3.4.3, EC 1.5.1.5, EC 3.5.4.9)
4) Bifunctional enzyme in eukaryotes (EC 1.5.1.15, EC 3.5.4.9)

Cellular Folate Transport Systems

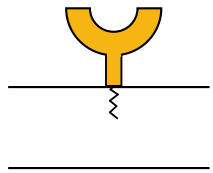
Reduced Folate Carrier (RFC)



- Organic anion antiporter
- Major folate transport system

Type:	Integral membrane glycoprotein, 12 transmembrane domains
pH Optimum:	7.4
Tissues:	Placenta, liver, leukocytes, kidney, lung, bone marrow, intestine, CNS, brain
Affinities:	(6S)-5-CH_3-H_4PteGlu (~ 5 µM) >> PteGlu (~ 200 µM)
Synonym:	Solute carrier family 19 member 1

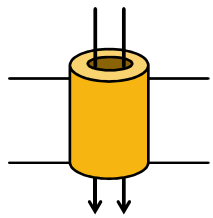
Folate Receptor (FR)



- Transport via receptor mediated endocytosis
- Expressed on the cell surface

Type:	Anchored to cell surface by a glycosylphosphatidylinositol (GPI) domain
Isoforms:	FR-α, FR-β, FR-γ (secreted), FR-δ
Tissues:	FR-α: Epithelial tissues (e.g. placenta, proximal renal tubular cells, choroid plexus) FR-α levels are greatly elevated in malignant tissues FR-β: Hematopoietic tissues (e.g. spleen, thymus, bone marrow), macrophages, fetal brain FR-γ: Hematopoietic tissues (e.g. spleen, thymus, bone marrow) FR-δ: Regulatory T-cells, Oocytes
Affinities:	(6S)-5-CH_3-H_4PteGlu (≥ 1 nM) < PteGlu (< 1 nM)
Synonym:	Folate binding protein (FBP)

Proton-Coupled Folate Transporter (PCFT)



- Proton symporter
- Major transport system for intestinal folate absorption

Type:	Integral membrane glycoprotein, 12 transmembrane domains
pH Optimum:	5.5
Tissues:	Intestine, kidney, liver, placenta, spleen, brain, testis, lung
Affinities:	(6S)-5-CH_3-H_4PteGlu (~ 1 µM) = PteGlu (~ 1 µM)
Synonym:	Heme carrier protein 1 (HCP1), solute carrier family 46 member 1

ATP-Binding Cassette (ABC) Transporters

- ATP dependent translocation of a wide variety of substances across membranes
- Export of folates (e.g. MRP1-5 and BCRP)

Type:	Transmembrane protein
Affinities:	Low-affinity, high-capacity pumps

Folate History

1931 Lucy Wills discovers that macrocytic anaemia can be prevented by adding yeast to a diet otherwise lacking B vitamins

1941 Herschel K. Mitchell and colleagues suggest the name “Folic acid” (folium, Latin for leaf) for the factor responsible for growth stimulation of Streptococcus lactis isolated from spinach

1945 Tom D. Spies demonstrates that Folic acid cures megaloblastic anaemia during pregnancy

1946 Robert B. Angier and co-workers report the structure and synthesis of the Lactobacillus casei factor (Folic acid) isolated from liver

1950 Emanuel B. Schoenbach and colleagues observe that the toxic side effects of amethopterin (methotrexate) cancer therapy can be reversed by treatment with “citrovorum factor” (Leucovorin)

1962 Victor Herbert consumes a folate-deficient diet for several months, documenting the development of deficiency symptoms

1968 Martin C. Carey and colleagues report that oral Folic acid therapy significantly reduces homocysteine excretion in the urine of mentally-handicapped children with homocystinuria

1981 Richard W. Smithells and co-workers report a preventive effect on neural tube defects by a periconceptional vitamin supplementation containing Folic acid

1982 David Machover and colleagues demonstrate that (6R,S)-5-Formyltetrahydrofolate or “Folinic acid” (Leucovorin) increases the therapeutic efficacy of 5-fluorouracil in the treatment of advanced colorectal and gastritic adenocarcinomas

1991 Nicholas Wald demonstrates in a randomised double-blind prevention trial that Folic acid supplementation before pregnancy reduces the risk of neural tube defects by 70% in women who had previously given birth to a child with a neural tube defect

1991 Eprova AG succeeds in producing (6S)-5-Formyltetrahydrofolate (Levoleucovorin), the natural isomer of (6R,S)-5-Formyltetrahydrofolate (Leucovorin), in commercial quantities

1992 Andrew E. Czeizel finds that first occurrence of neural tube defects may be prevented by periconceptional Folic acid supplementation

1992 The U.S. Public Health Service recommends women of childbearing age to consume 0.4 mg of Folic acid daily

1997 Mary Ward and colleagues demonstrate that plasma homocysteine can be lowered by physiological doses of Folic acid

1998 The U.S. Food and Drug Administration (FDA) introduces mandatory fortification of flour, rice, pasta, and other grain products with Folic acid

2001 The U.S. Food and Drug Administration (FDA) accepts (6S)-5-Methyltetrahydrofolate (Metafolin®) for use in dietary supplements

2004 The European Food Safety Authority (EFSA) considers (6S)-5-Methyltetrahydrofolate (Metafolin®) safe

2005 The “Joint FAO/WHO Expert Committee on Food Additives” (JECFA) considers (6S)-5-Methyltetrahydrofolate (Metafolin®) safe

2008 The U.S. Food and Drug Administration (FDA) approves (6S)-5-Formyltetrahydrofolate (Fusilev®) for rescue after high-dose methotrexate therapy

2010 The U.S. Food and Drug Administration (FDA) approves Beyaz® a combination oral contraceptive containing (6S)-5-Methyltetrahydrofolate (Metafolin®) to prevent neural tube defects

2015 The Center for Radiopharmaceutical Sciences (CRS), a joint endeavor between the Paul Scherrer Institute, the ETH Zurich and the University Hospital Zurich starts the first-in-man clinical trial with a novel folate-based [^{18}F]-PET tracer for imaging of folate receptor-positive tumors

2018 Isofol Medical AB reports positive efficacy data for (6R)-5,10-Methylenetetrahydrofolate (Modufolin®) from patients treated for metastatic colorectal cancer

SAFC®

Pharma & Biopharma Raw Material Solutions

MilliporeSigma
400 Summit Drive
Burlington, MA 01803, USA

EMDMillipore.com

The typical technical data above serve to generally characterize the product. These values are not meant as specifications and they do not have binding character. To learn more about the product specifications and to place an order, please send an e-mail to **folates@emdmillipore.com**

We provide information and advice to our customers on application technologies and regulatory matters to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect of any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.purpose.

For additional information, please visit EMDMillipore.com
To place an order or receive technical assistance, please visit EMDMillipore.com/contactPS

For more information please contact:
Phone: +41 52 630 72 72
E-mail: folates@emdmillipore.com

Lit. No. MS_BR2972EN Ver. 1.0
2018-11753 05/2018