B12
Folic acid

DR PRADNYA ROTITHOR

B complex vitamins

- Vitamin B_1 (Thiamine)
- Vitamin B_2 (Riboflavin)
- Vitamin B_3 (Niacin or niacinamide)
- Vitamin B_5 (Pantothenic acid)
- Vitamin B_6 (Pyridoxine, pyridoxal or pyridoxamine or pyridoxine hydrochloride)
- Vitamin B_7 (Biotin)
- Vitamin B_9 (Folic acid)
- Vitamin B_{12} (Cobalamines – cyanocobalamin)

- Deficiency of B12 and folic acid results in megaloblastic anaemia
- Characterized by large sized (mega) RBCs which are short lived.
- Hence b12 and fa are termed maturation factors


DIETARY SUPPLEMENT
natural Factors
Vitamin
B12
1000 mcg
60 Tablets
CYANOCOBALAMIN
Folic acid
Folic Acid 5mg Tablets

B12	Folic acid
----------not synthesized by humans---------- -------GIT flora does synthesize but NOT absorbed ----------	
Fish, meat, liver, eggs, milk	Green leafy, fruit, milk, meat, eggs
Requirement: 2-3 mcg / day	Requirement: 50 mcg/day Pregnancy, lactation: 200-300 mcg
Cyano- or hydroxocobalamin 100-1000 mcg/day – alternate days x 2 wks, then every month IM for severe, PO for mild **Pernicious: always parenteral: lifelong: later every 3 months**	1-5 mg every day PO – mild deficiency 5-10 mg severe deficiency

VITAMIN B12 (cobalamin)

- B12 + Intrinsic factor of Castle (parietal cells) → absorption (ileum)
- Stored in liver
- Plasma transport: bound to Transcobalamin II

- Daily requirement: 1-3 mcg: (dietary deficiency rare)
- Pregnancy, lactation: 3-5 mcg

hydroxocobalmin, cyanocobalmin

- Hydroxocobalmin, Cyanocobalmin- injections
- Methylcobalamin tablet: 0.5 mg

Vit B12 is synthesized in nature only by microorganisms

Plants and animals including humans acquire it from them

The ONLY source for pure veg people --sprouted pulses

- ORAL
- PARENTERAL
- - for severe deficiency
- - for PERNICIOUS ANEMIA

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Indications - B12

- **Treatment of deficiency**
- **Treatment and prevention of deficiency in patients with predisposing factors -** gastric mucosal damage: chronic gastritis, gastric carcinoma, gastrectomy --Malabsorption – diseases of ileum -bowel resection-surgical removal of ileum -fish tape worm infestation
- **Pregnancy, lactation—increased requirement**
- **Neuropathies, psychiatric disorders, diabetes, alcoholism, Tobacco amblyopia**

Metabolic functions of B12

Intricately linked with folate metabolism

Active coenzymes forms of b12 –

methyl B12 and DAB12 (deoxyadenosyl)

-methyl B12 --needed for conversion of homocysteine to methionine

This reaction is critical in making THFA available for reutilization

Deficiency of b12 results in THFA getting trapped in methyl form and reactions needing one carbon transfer suffer

This is called folate trap

Purine and pyrimidine synthesis is affected due to this trap

B12 functions contiued

Melanoic acid -------DAB12-------succinic acid

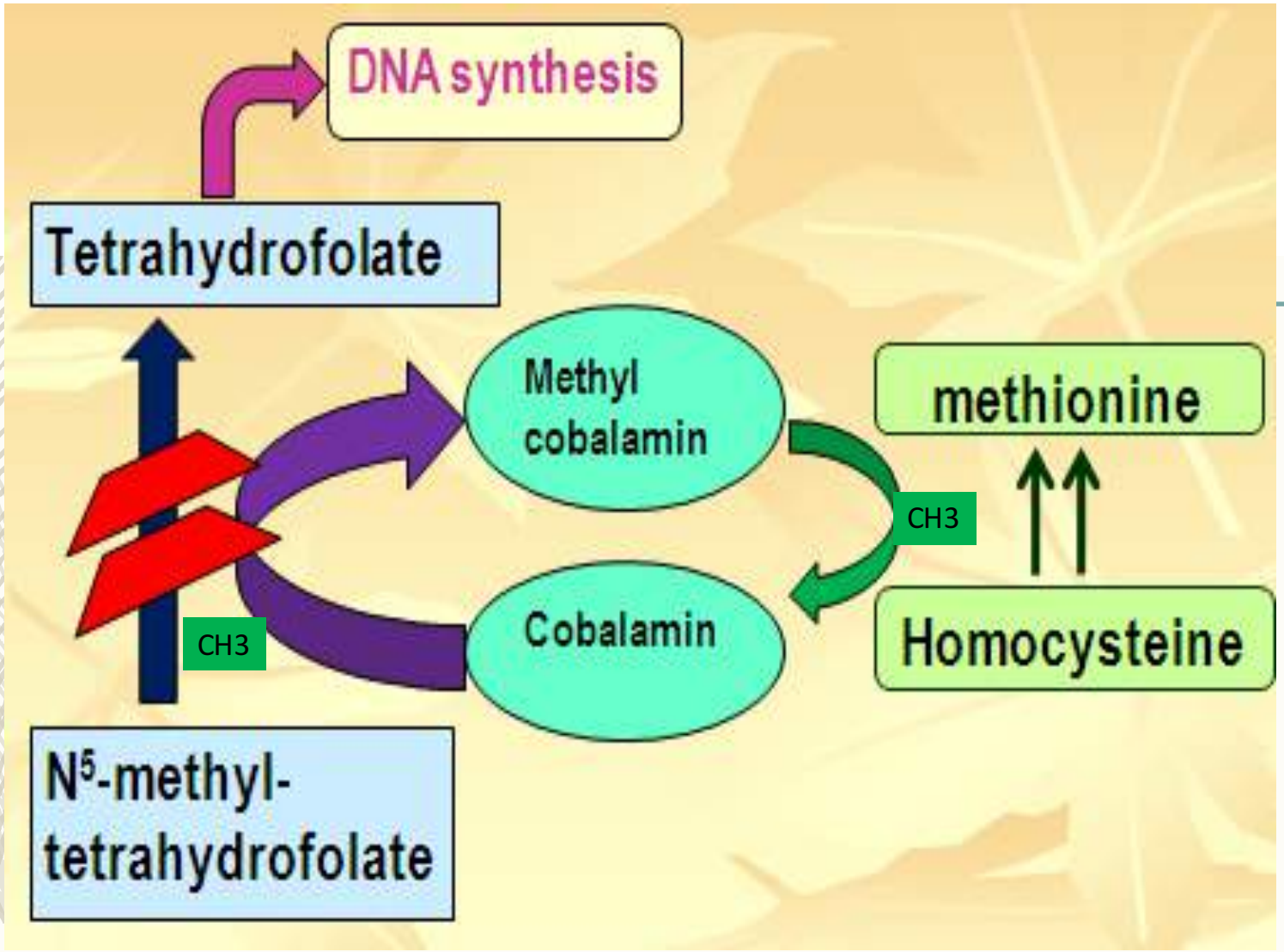
Links cbh and lipid metabolisms

Lack of this reaction results in demyelination of nerves seen in B12 deficiency

This reaction does NOT involve folic acid

Methionine ---DAB12 ----s adenosyl methionine

This reaction appears to be more imp in nerve damage of b12 deficiency as it is needed in formation of myelin and phospholipids


DNA synthesis
Tetrahydrofolate
Methyl cobalamin
methionine
CH3
Cobalamin
Homocysteine
CH3
N5-methyl-tetrahydrofolate

B12 deficiency manifestations

B12 & folate: together termed as maturation factors

Cofactor (transfer of 1-carbon units) → DNA synthesis

Deficiency:

1)First manifests as megaloblastic anemia—

indistinguishable to identify whether caused by either FA or B12

Impaired DNA synthesis and mitosis in precursor RBCs

↓ No of mature RBCs, RBCs

-↑ size / ↓ life span / prone to hemolysis

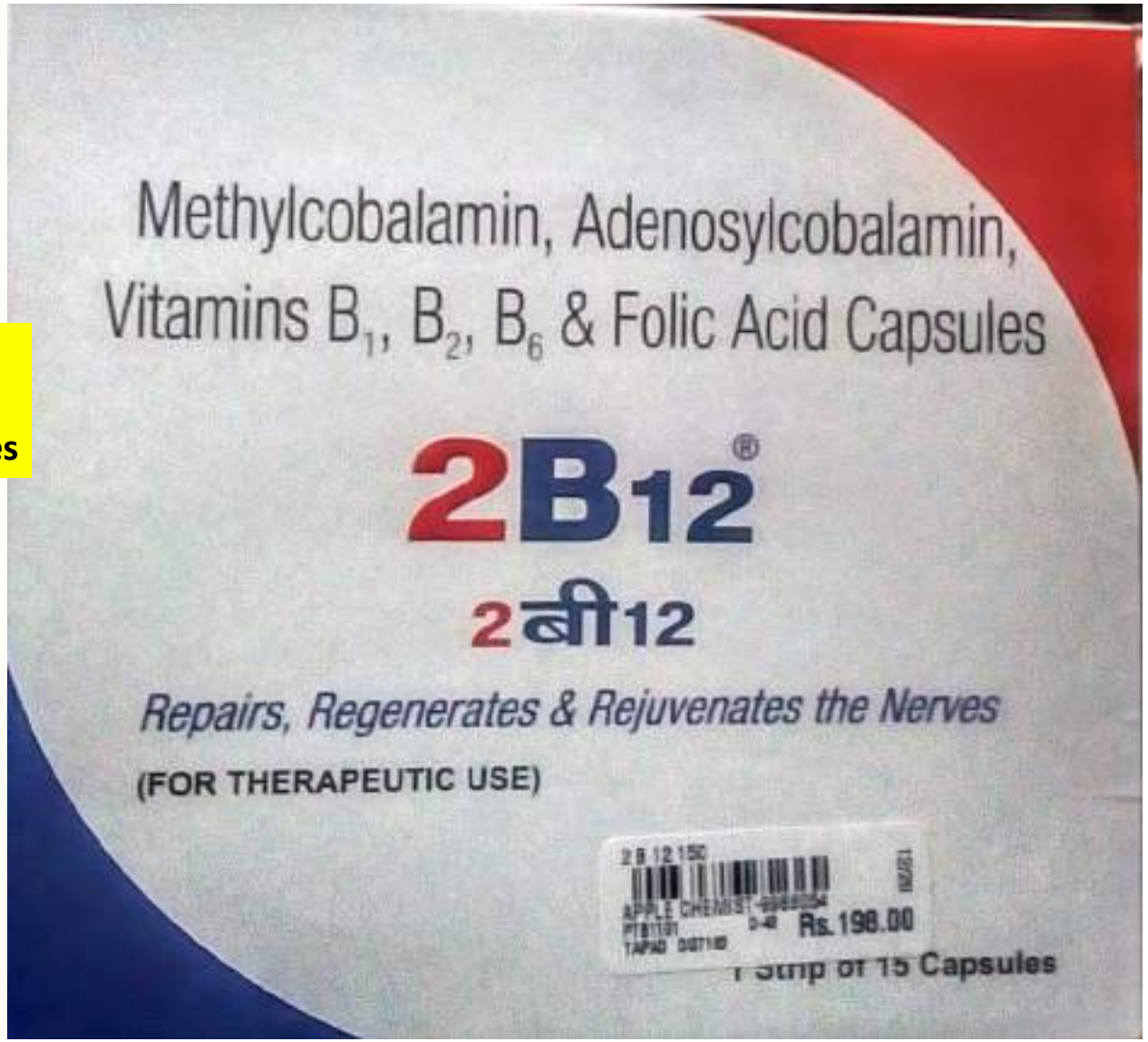
2)neurologic defects (paresthesia, weakness, fatigue)

Memory loss mood changes

-3)glossitis ,GIT disturbances : epithelial damage

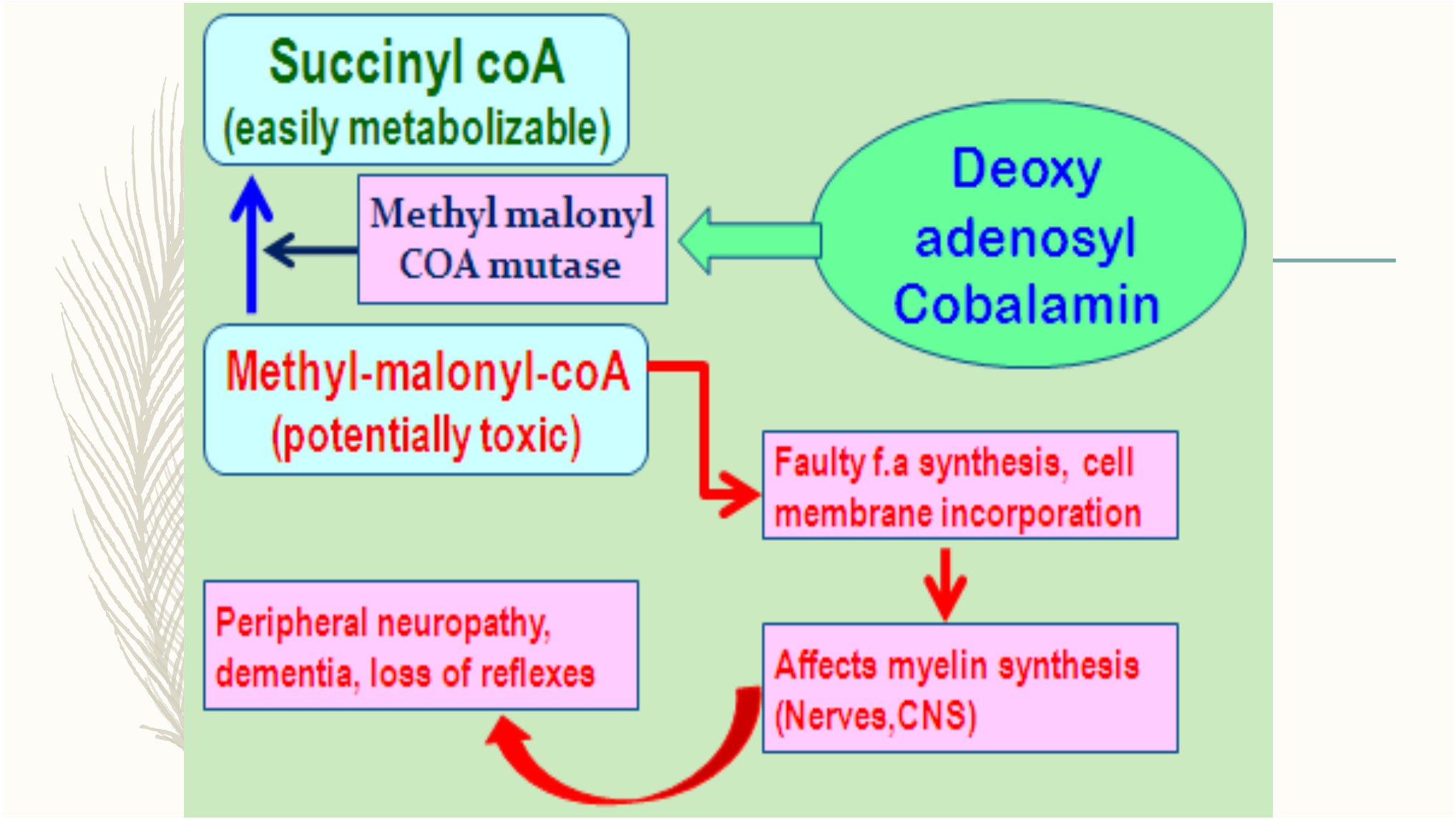

50 x 1 ml Ampoules
VITAMIN B12
1000 mcg
INJECTION
Each ml contains :-
CYANOCOBALAMIN U.S.P.
1000 mcg
FOR INTRAMUSCULAR USE
T P
Manufactured by
T.P. DRUG LABORATORIES
(1969) CO.,LTD.
98 Soi Sukhumvit 62 Yak 1, Bangchak,
Prakanong, Bangkok 10260
Tel. 0 2311 1911-3
Fax. 0 2331 9018

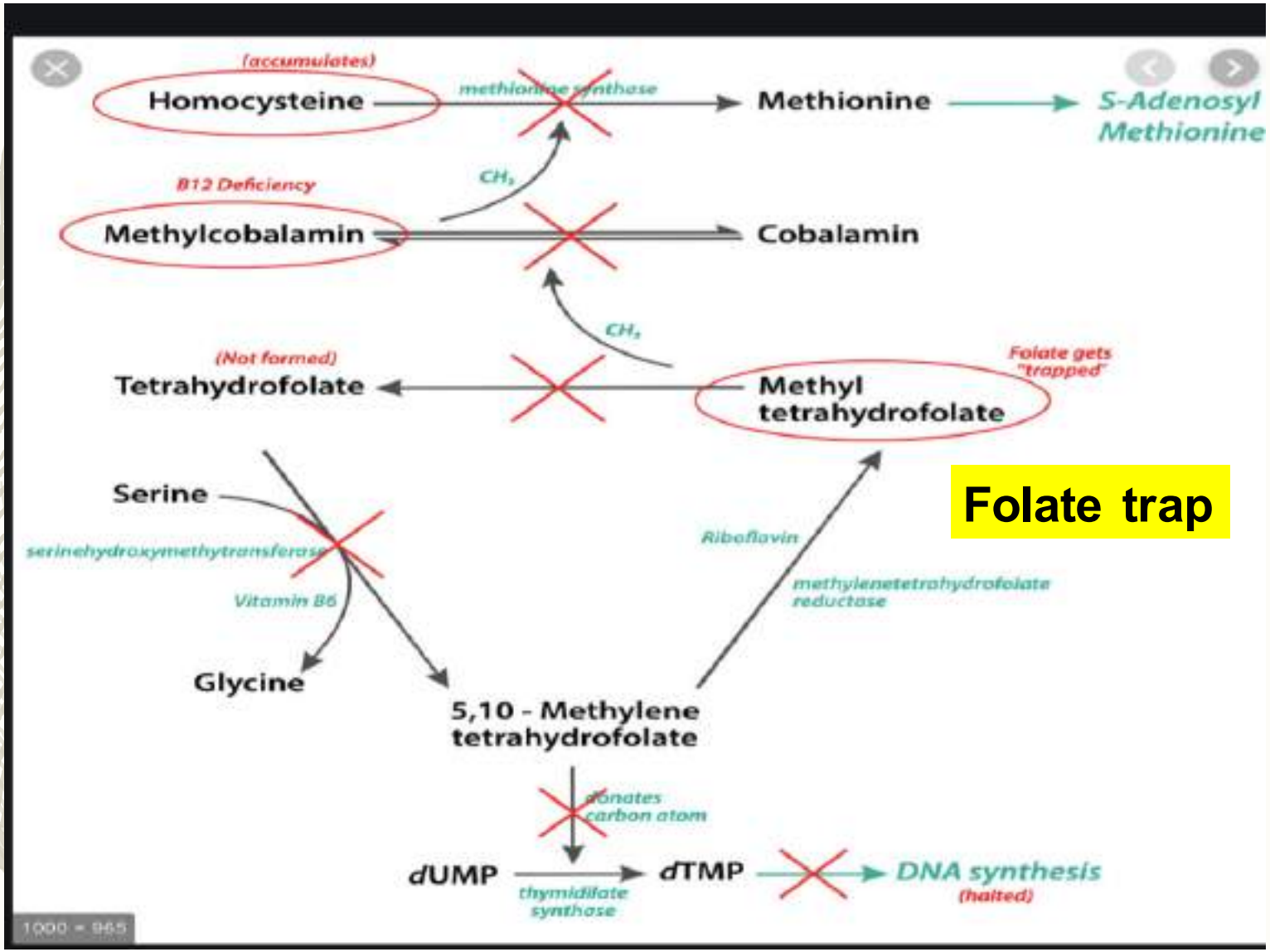
Diabetic ,alcoholic
and
other forms of peripheral neuropathies



Addisonian pernicious anemia

- Hereditary autoimmune disease → parietal cell destruction
- OR
- Antibodies against intrinsic factor
- -bind to intrinsic factor and prevent B12 binding
- or
- -bind to IF-B12 complex, prevent binding of complex to IF receptors on ileum


Succinyl coA
(easily metabolizable)
Methyl malonyl COA mutase
Deoxy adenosyl Cobalamin
Methyl-malonyl-coA
(potentially toxic)
Faulty f.a synthesis, cell membrane incorporation
Peripheral neuropathy, dementia, loss of reflexes
Affects myelin synthesis (Nerves,CNS)


(accumulates)
Homocysteine
methionine synthase
Methionine
S-Adenosyl Methionine
B12 Deficiency
CH_3
Methylcobalamin
Cobalamin
CH_3
(Not formed)
Tetrahydrofolate
Folate gets "trapped"
Methyl tetrahydrofolate
Serine
serinehydroxymethytransferase
Vitamin B6
Glycine
Riboflavin
methylenetetrahydrofolate reductase
5,10 - Methylene tetrahydrofolate
donates carbon atom
dUMP
thymidilate synthase
dTMP
DNA synthesis
(halted)
1000 - 965

Folate trap

Giving folate in B12 deficiency

- Folate helps to refill the tetrahydrofolate pool, to ------
- Partially or fully corrects the anemia

- But exogenous folate CANNOT CORRECT the NEUROLOGIC defects due to B12 deficiency.

- Anemia may improve, but neurologic signs worsen !!!

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----------not synthesized by humans----------	
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Requirement: 2-3 mcg / day	Requirement: 50 mcg/day Pregnancy, lactation: 200-300 mcg
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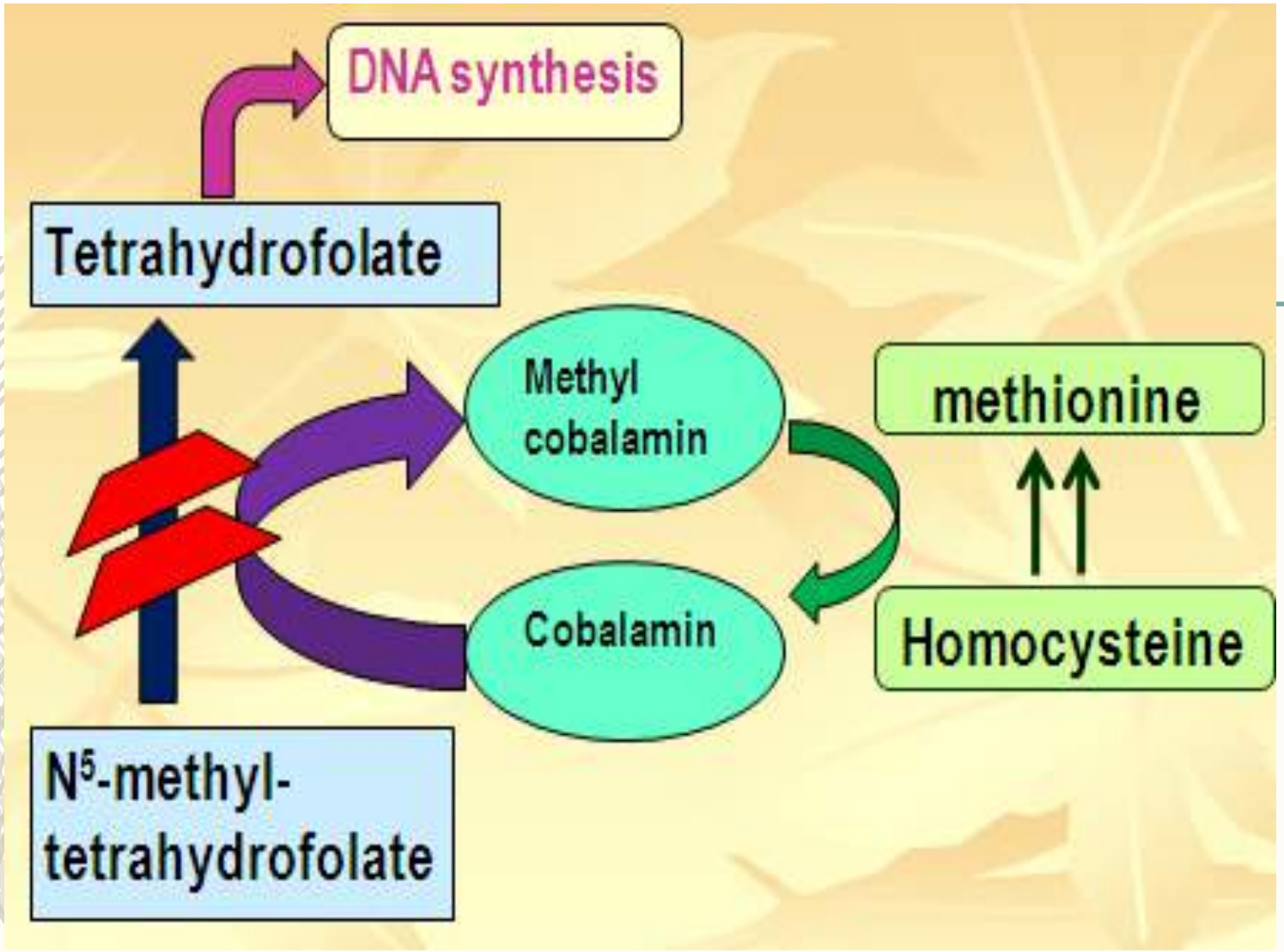
Folic acid

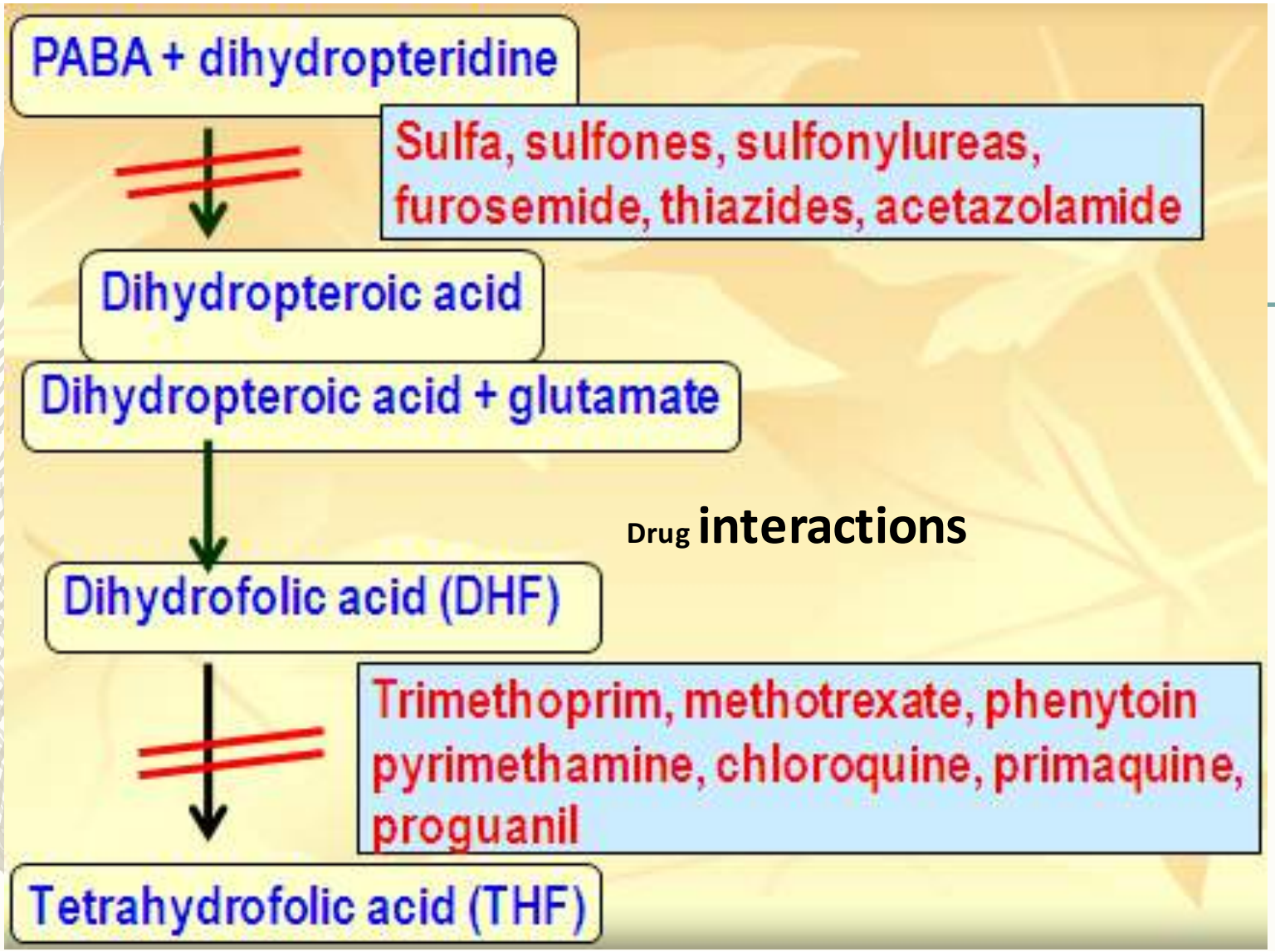
- Deficiency: Megaloblastic anemia
- Pregnancy: Neural tube defects
- Interconvertible forms:
- 5-THF (folinic acid), 10-formyl THF, 5,10 methylene THF
- Serve as carbon donor in various 1-carbon-transfer reactions by carrying a methyl group as adduct
- oxidation, DNA synthesis

- Remember – Link between folate & B12
- Methyltetrahydrofolate → tetrahydrofolate


DNA synthesis
Tetrahydrofolate
Methyl cobalamin
methionine
Cobalamin
Homocysteine
N5-methyl-tetrahydrofolate

Folic acid – mild 1-5 mg/day, severe 5-10 mg /day

- **Indications –**
  - Megaloblastic anemia due to dietary deficiency
  - Malabsorption states
  - Pregnancy, lactation
  - Liver disease, dialysis
  - Methotrexate toxicity – treat and prevent
  - Phenytoin toxicity
  - Chronic alcohol ingestion



Drug **interactions**

Folinic /leucovorin rescue / citrovorum rescue

- **Preventing toxicity of high dose Mtx**
- IV methtrexate
- Then within ½- 1 hour –
- Folinic acid (5 formyl THFA) 1-3 mg IV

- ***Rescue the NORMAL Cells of the body.***

Haemopoietic growth factors Notable features --

All hematopoietic growth factors are –

Proteins with MW > 15,000.

Oral administration not possible

Their peptide bonds are destroyed by gastric acid and digestive enzymes.

Hemopoietic growth factors

- 1. Erythropoietin (Epoetin)(r Hu Epo) (recombinant Human Epoetin)
- 2. Granulocyte colony stimulating factor (G-CSF) (r Hu G-CSF) (Filgrastim)
- 3. Granulocyte-Macrophage colony stimulating factor (GM-CSF) - r Hu GM-CSF (Sargramostim)
- 4. Megakaryocyte growth factor (Interleukin - 11): Oprelvekin

No effect on RBC life span

MOA :-

EPO receptor on RBC progenitors and stimulates RBC production and Hb formation

Dose dependent induction of erythropoiesis

Erythropoietin

MW 34000

Peritubular cells of kidney

In response to hypoxia and anaemia

Essential for normal erythropoiesis

Hemopoietic growth factors

1. Erythropoietin (Epoetin)(r Hu Epo)

(recombinant Human Epoetin). EPO alpha and EPO beta

Primary indication –

Chronic renal failure-to increase the haemoglobin concentration. Reduces need for blood transfusions

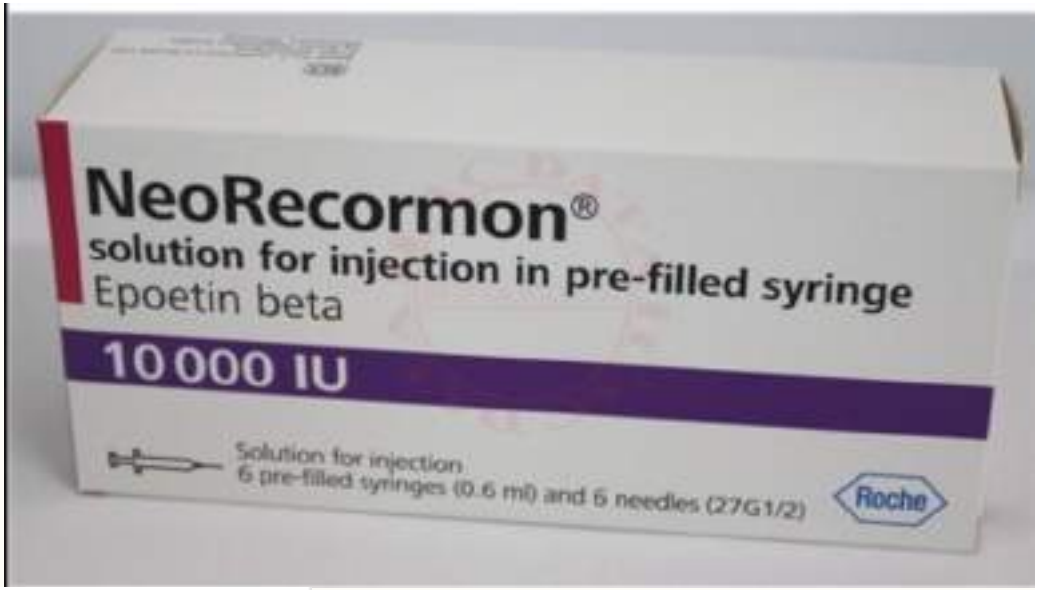
(50-150 IU per kg subcutaneously 3 times a week—EPO alpha max dose 600 IU/kg/wk)

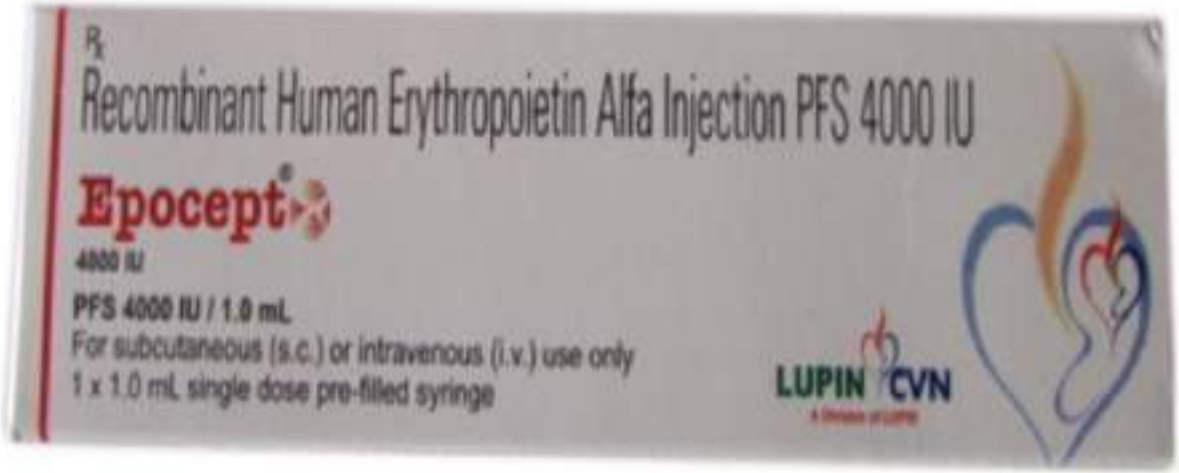
EPO beta long half life –to be given once in 2-4 wks

Other indications--

Aplastic anemia, multiple myeloma

AIDS, cancers, zidovudin-induced anaemia


NeoRecormon®
solution for injection in pre-filled syringe
Epoetin beta
10 000 IU
Solution for injection
6 pre-filled syringes (0.6 ml) and 6 needles (27G1/2)
Roche


℞
Recombinant Human Erythropoietin Alfa Injection PFS 4000 IU
Epocept®
4000 IU
PFS 4000 IU / 1.0 mL
For subcutaneous (s.c.) or intravenous (i.v.) use only
1 x 1.0 mL single dose pre-filled syringe
LUPIN CVN

Adverse effects

nonimmunogenic

Sudden rise in haematocrit
Blood viscosity
Hypertensive episodes
Sudden clot formations in AV shunts

Hemopoietic growth factors

- 2. Granulocyte colony stimulating factor (G-CSF) (r Hu G-CSF) (Filgrastim)

- 3. Granulocyte-Macrophage colony stimulating factor (GM-CSF) - r Hu GM-CSF (Sargramostim)

- **Cancer chemotherapy-induced neutropenia, aplastic anemia, stem cell transplantation, bone marrow transplantation**

- ***GM-CSF is more toxic than G-CSF.***

Hemopoietic growth factors

- **4. Megakaryocyte growth factor (Interleukin -11): Oprelvekin**

- **Thrombocytopenia: Treatment & prevention**
- **(cancer chemotherapy induced thrombocytopenia)**