Vitamine

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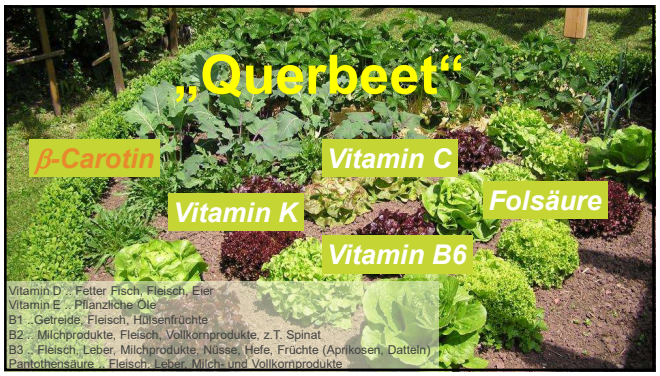
Geschichte der Vitamine

- 19. Jahrhundert: Protein, Kohlenhydrate, Fette und Mineralien als Nährstoffe erkannt
- Pasteur & Koch: „germ theory“ – meiste Erkrankungen, z.B. auch Rachitis, Skorbut, infektionsbedingt
- Hopkins, 1906: „Accessory factor“ – junge Ratten wachsen, wenn Fett, Protein und Stärke eine kleine Menge Milch zugeführt wird
- Funk, 1912: Bezeichnung der „Accessory factors“ als Vitamine und Beschreibung von Beriberi, Pellagra und Skorbut als Vitaminmangelerkrankungen

Semba RD. The discovery of the vitamins. Int. J. Vitam. Nutr. Res., 82: 310, 2012



Mikronährstoffstatus von „Omnivoren“, „Vegetariern“ und „Veganern“ in der Schweiz

Vitamin	OV (n=100)	VEG (n=53)	VEGAN (n=53)
Vitamin A	1.0	0.0	3.8
Vitamin E	0.0	0.0	3.8
Vitamin B1	4.2	1.1	1.4
Vitamin B2	14.0	22.6	26.4
Niacin	11.0	34.0	26.4
Vitamin B6	29.0	58.5	24.5
Folat	58.0	30.2	13.2
Pantothensäure	6.0	13.2	7.5
Biotin	16.0	15.1	7.5
Vitamin B12	1.0	5.7	7.5
Vitamin C	12.0	3.8	3.8
Iod	64.5	66.0	78.8

% mit ungenügender Versorgung

Schüpbach R et al., Eur J Nutrition, epub 2016

NUTRITION

Are mild maternal iodine deficiency and child IQ linked?

Michael B. Zimmermann

A recent observational study from the UK has reported lower IQ and poorer school performance in children born to iodine-deficient mothers than in children whose mothers were iodine-sufficient. These findings add to growing evidence that even mild-to-moderate maternal iodine deficiency impairs the cognitive development of the child.

Zimmermann, M. B. *Nat. Rev. Endocrinol.* advance online publication 2 July 2013; doi:10.1038/nrendo.2013.128

Mikronährstoffversorgung in der Schwangerschaft

Kein Jod !

150 – 200 µg Jod

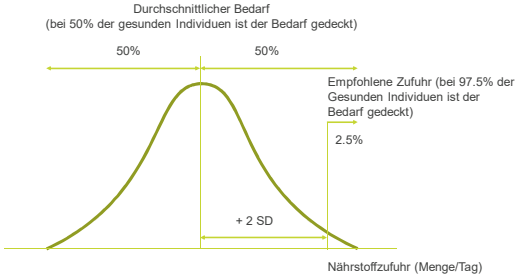
Beipackzettel

Burgerstein Multivitamin-Mineral CELA (Tagesportion = 2 Tabletten) enthält:

Vitamin A	800 µg	100%*	Folsäure	600 µg	300%*
Vitamin D3	5 µg	100%*	Kalzium	240 mg	30%*
Vitamin E	12 mg	100%*	Magnesium	120 mg	32%*
Vitamin K	75 µg	100%*	Eisen	14 mg	100%*
Vitamin C	240 mg	300%*	Zink	10 mg	100%*
Vitamin B1	1,1 mg	100%*	Selen	55 µg	100%*
Vitamin B2	1,4 mg	100%*	Kupfer	1 mg	100%*
Vitamin B6	1,4 mg	100%*	Jod	150 µg	100%*
Vitamin B12	2,5 µg	100%*	Mangan	2 mg	100%*
Niacin	16 mg	100%*	Molybdän	50 µg	100%*
Pantothensäure	6 mg	100%*	Chrom	40 µg	100%*
Biotin	150 µg	300%*			

** Anteil der vom BLV empfohlenen Tagesdosis (ETD)*

„Empfohlene Zufuhr“ und *„durchschnittlicher Bedarf“*



D-A-CH

- Referenzwerte für die Nährstoffzufuhr der
- Deutschen Gesellschaft für Ernährung
- Österreichischen Gesellschaft für Ernährung
- Schweizerischen Gesellschaft für Ernährung
- http://www.sge-ssn.ch

Empfohlene Zufuhr gemäss D-A-CH

(exemplarisch für 51-65 jährige Erwachsene)

Vitamin	m	w	Vitamin	m	w
Vitamin A (mg) Retinol	1.0	0.8	Vitamin B6 (mg) Pyridoxin	1.5	1.2
Vitamin D (µg) Calciferol	20		Folat (µg)	300	
Vitamin E (mg) Tocopherol	13	12	Pantothensäure (mg)	6	
Vitamin K (µg)	80	65	Biotin (mcg)	30-60	
Vitamin B1 (mg) Thiamin	1.2	1.0	Vitamin B12 (µg) Cobalamine	3.0	
Vitamin B2 (mg) Riboflavin	1.3	1.0	Vitamin C (mg)	110	95
Niacin (mg)	15	11			

Vergleich verschiedener Vitaminpräparate

Vitamin	Empfohlene Zufuhr		Supradyn energy	Actilife All in one	Centrum	Becozym forte
Vitamin A (mg)	1.0	0.8	0.8	0.4	0.8	
Vitamin D (µg)	20		5	2.5	5	
Vitamin E (mg)	13	12	10	12	15	
Vitamin K (µg)	80	65	30		30	
Vitamin B1 (mg)	1.2	1.0	4.2	1.1	1.4	15
Vitamin B2 (mg)	1.3	1.0	4.8	1.4	1.75	15
Niacin (mg)	15	11	54	16	20	50
Vitamin B6 (mg)	1.5	1.2	6	1.4	2.0	10
Folat (µg)	300		600	200	200	
Pantothensäure (mg)	6		18	6	7.5	25
Biotin (µg)	30-60		450	50	62.5	150
Vitamin B12 (µg)	3.0		3.0	2.5	2.5	10
Vitamin C (mg)	110	95	180	80	100	

Wer von ihnen hat in den letzten Monaten ein Nahrungsergänzungsmittel, inkl. Multivitamine, eingenommen ?

„Epidemiologie“ von Nahrungsergänzungsmitteln und Multivitaminpräparaten

Autor	Land	Studie	Methode	Nahrungs-ergänzung	Multivitamin
Bailey et al., 2011	USA	NHANES	Fragebogen	F: 53% M 44%	F: 36% M: 31%
Sakur et al., 2012	Canada	CCHS 2.2	Interview	F+M: 40%	F+M: 28%
Lentjes et al., 2015	UK	EPIC-Norfolk	Ernährungs-protokoll	F: 46% M: 35%	
Messerer et al., 2001	Schweden	Bevölkerung	Interview	F: 33% M: 22%	
Li et al., 2010	Deutschland	EPIC-Heidelberg	Interview	F: 39% M: 29%	
Pouchieu et al., 2013	Frankreich	NutriNet-Santé	Fragebogen	F: 46% M: 24%	

Vitamine, Krebsrisiko und kardiovaskuläres Risiko

Vitaminsupplemente und Gesamtmortalität

Vitamin	Anzahl Studien	Beobachtungs dauer	RR (95% CI)	Bemerkung
Multivitamin	3	3-12.5	0.95 (0.89-1.01)	
β-Caroten	5	4.1-16	1.05 (1.02-1.08)*	
Vitamin A	1	5	1.15 (0.81-1.08)	
Vitamin E	5	3 -16	1.01 (0.98-1.04	
Vitamin C	2	3-8	1.06 (0.97-1.16)	
Folsäure	1	10	0.52 (0.24-1.10)	

Fortmann SP et al., Ann Intern Med 159: 824, 2013; Rautiainen S et al. Nat Rev Endocrinol 12: 407, 2016

Vitaminsupplemente und Krebsrisiko bei gesunden Personen

Vitamin	Anzahl Studien	Beobachtungs dauer	RR (95% CI)	Bemerkung
Multivitamin	2	11.2-12.5	0.94 (0.89-1.00)	PHS II: US Ärzte Krebsinzidenz ↓8% 27%↓Krebsrezidive SUVIMAX: FRA 31%↓Krebsrisiko bei.?
β-Caroten	2	4.1-12.9	0.98 (0.92-1.05)	18% erhöhtes Lungenca.-Risiko nach Asbestexposition
Vitamin D	2	5-6.2	1.05 (0.94-1.18)	
Vitamin E	3	8-12	1.03 (0.99-1.08)	
Vitamin C	1	8	1.00 (0.92-1.09)	
Folsäure	1	10	1.65 (1.09-2.51)	

Fortmann SP et al., Ann Intern Med 159: 824, 2013; Rautiainen S et al. Nat Rev Endocrinol 12: 407, 2016

Vitaminsupplemente und kardiovaskuläres Risiko

Vitamin	Anzahl Studien	Beobachtungs dauer	RR (95% CI)	Bemerkung
Multivitamin	2	11.2-12.5	1.02 (0.94-1.10)	
β-Caroten	2	4.1-12.9	1.01 (0.93-1.09)	
Vitamin D	2	5-6.2	0.94 (0.87-1.02)	
Vitamin E	2	5-8	0.97 (0.92-1.03)	
Vitamin C	1	8	0.99 (0.89-1.10)	
Hochdosierte B12, B6, Folsäure-Kombinationen		Keine Reduktion von CV-Ereignissen trotz Reduktion der Homocysteinserumkonzentration		

Fortmann SP et al., Ann Intern Med 159: 824, 2013; Rautiainen S et al. Nat Rev Endocrinol 12: 407, 2016

Kein Effekt einer Substitution mit 0.4 mg B12, 0.8 mg Folsäure und 40 mg B6 auf das cv Risiko nach MI

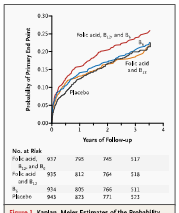


Figure 1. Kaplan–Meier Estimates of the Probability of Reaching the Primary End Point during Follow-up.
The primary end point was a composite of fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and sudden death attributed to coronary heart disease.

Table 2. Plasma Levels of Total Homocysteine and B Vitamins at Baseline, after Two Months, and at the End of the Intervention.*

Variable	Folic Acid, B_{12}, and B_6 (N=337)†	Folic Acid and B_{12} (N=333)‡	B_6 (N=334)§	Placebo (N=343)¶
Total homocysteine (μmol/liter)				
Baseline	13.1±5.0	12.9±4.3	13.3±6.1	13.2±5.2
2 Mo	9.4±3.0	9.5±2.8	13.7±5.7	13.7±5.6
End of intervention	9.5±3.6	9.8±4.0	13.3±5.4	13.6±6.2
Folate (nmol/liter)				
Baseline	13.1±27.5	11.7±28.4	9.4±6.6	9.6±6.0
2 Mo	59.9±29.5	68.2±30.0	7.9±7.1	9.9±6.3
End of intervention	61.8±31.7	70.4±36.4	10.4±9.6	13.1±14.5
Vitamin B_{12} (pmol/liter)				
Baseline	388±161	400±311	388±167	383±182
2 Mo	571±212	578±372	398±158	393±143
End of intervention	638±370	648±414	398±320	390±171

Bonaa KH et al., N Engl J Med 354:1578, 2006

Vitaminsupplementation und Krebsrisiko und kardiovaskuläre Mortalität

- Niedrigdosierte Multivitamine (ca. empfohlene Zufuhr) senken möglicherweise die Krebsinzidenz, v.a. bei Männern mit einem vorbestehenden Karzinom und bei vorbestehend unzureichender Versorgung mit Vitamin E und C.
- Eine hochdosierte Substitution mit individuellen Vitaminen, β-Caroten, Vitamin E, Folsäure, Vitamin C haben keinen positiven Effekt auf das Krebsrisiko und die kardiovaskuläre Mortalität.
- Hochdosiertes β-Caroten, Vitamin E und Folsäure haben möglicherweise schädliche Effekte.

Vitamine und kognitive Funktion

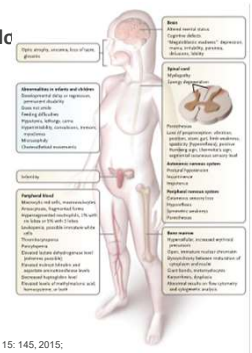
Vitamine und kognitive Funktion

Inhaltstoffe:
- Hydroxocobalaminum 0,5 mg,
- L-O-Phosphothreoninum 10 mg,
- L-Glutaminum 60 mg

Indikation gem. Compendium
- Herabgesetzte körperliche und geistige
- Leistungsfähigkeit
- Müdigkeit
- Konzentrationsschwäche
- nervöse Verspannung
- Rekonvaleszenz

Vitamin B12-Mangel – Epidemiolo & Klinik

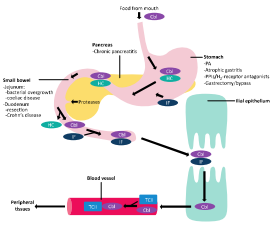
- Alter > 60 Jahre – 20%, < 60 4%
- Perniziöse Anämie
  - Medianes Alter 70-80 Jahre
  - Prävalenz ca. 4%
  - Milde Formen bis zu 20%
- Gastrektomie
- Bariatrische Chirurgie
- Ileumresektion, Blind-loop
- Parasiten
- Medikmente
  - Metformin
  - PPI, H2-Blocker
- Ungenügende Zufuhr
  - Vegetarier, Veganer
  - Mangelernährung



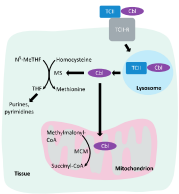
Stabler EP, N Engl J Med 368:149, 2013; Shipton MJ, Clinical Medicine 15: 145, 2015;

Vitamin B12-Mangel - Pathophysiologie

Resorption und Transport



Intrazellulärer Metabolismus



Welche Parameter bestimmen Sie zur Beurteilung eines B12-Mangels ?

Vitamin B12-Mangel - Diagnose

- Vitamin B12 Konzentration
  - Cut-offs: 100 – 350 pmol/l, 37% 148 bzw. 150 pmol/l
- Holo-Transcobalamin
  - Cut-offs: 20-50 pmol/l
- Methylmalonsäure
  - Cut-offs: 0.21-0.47 µmol/l
- Homozystein
  - Cut-offs: 10-21.6 µmol/l

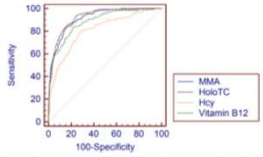


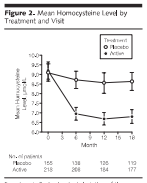
Fig. 3 Receiver operating characteristic (ROC) curves of vitamin B12, holoTC, MMA and Hcy. The Fedosov wellness parameter $\omega = -0.5$ was used as a separator of the groups assumed deficient and assumed healthy

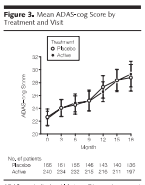
Referenzbereiche für Personen (637 m/506 f) > 60 Jahre

Holo-TC	23-110 pmol/l
Vitamin B12	119-465 pmol/l

Risch M et al. BMC Geriatrics 15: 82, 2015
Aparicio-Ugarriza et al., Clin Chem Lab Med 53: 1149, 2015

High-Dose B Vitamin Supplementation and Cognitive Decline in Alzheimer Disease





- 5 mg Folsäure und
- 1 mg B12 und
- 25 mg B6
- vs. Placebo

Aisen PS et al. *JAMA 300(15):1774, 2008*

Effects of vitamin B-12 supplementation on neurologic and cognitive function in older people: a randomized controlled trial (1 mg, 18 mo)

TABLE 4
Effects of vitamin B-12 on serum concentrations of vitamin B-12, holotranscobalamin, homocysteine, folate, and hemoglobin[1]

	Vitamin B-12					Placebo			
Serum measure	n	Baseline	12 mo	Change from baseline, %	n	Baseline	12 mo	Change from baseline, %
Vitamin B-12, pmol/L	74	231.3 ± 52.0[2]	640.9 ± 199.3	177	70	238.4 ± 60.7	235.7 ± 77.5	0
Holotranscobalamin, pmol/L	71	55.7 ± 21.5	240.0 ± 162.9	331	70	51.8 ± 17.5	54.2 ± 20.5	5
Homocysteine, µmol/L	73	17.7 ± 4.6	14.2 ± 4.2	−17	70	17.2 ± 5.6	17.4 ± 6.0	1
Folate, nmol/L	72	20.7 ± 12.3	20.2 ± 11.6	−2	71	21.0 ± 13.8	20.4 ± 14.0	−3
Hemoglobin, g/L	78	140.5 ± 11.0	140.0 ± 10.7	0	71	137.9 ± 12.8	137.2 ± 12.6	0

[1]Small amounts of missing data (n < 10/analysis).
[2]Mean ± SD (all such values).

TABLE 6
Effects of vitamin B-12 on cognitive and psychological function outcomes at 12 mo

	Vitamin B-12 (n = 91)	Placebo (n = 93)	Unadjusted effect size[2]	Adjusted effect size[2]
California Verbal Learning Test				
Total words correct in first 5 trials, n	23.9 ± 0.7[2]	24.6 ± 0.7	−1.4 (−2.9, 0.1)[3]	−1.4 (−2.9, 0.1)
Words recalled at delayed recall, n	7.5 ± 0.3	7.7 ± 0.4	−0.4 (−1.0, 0.2)	−0.4 (−1.0, 0.2)
Symbol letter modality, n correct	39.6 ± 1.1	40.1 ± 1.2	−1.5 (−5.2, 0.6)	−1.5 (−5.2, 0.6)
Reaction time, s				
Simple	0.3 ± 0.01	0.3 ± 0.01	0.01 (−0.02, 0.04)	0.01 (−0.02, 0.04)
Choice	0.7 ± 0.01	0.7 ± 0.02	−0.003 (−0.03, 0.02)	−0.003 (−0.03, 0.02)
Verbal fluency, n animals named	20.8 ± 0.5	19.9 ± 0.6	1.1 (−0.1, 2.2)	1.1 (−0.1, 2.2)
30-item General Health Questionnaire score[4]	2.4 ± 0.5	2.7 ± 0.5	−0.1 (−1.2, 1.0)	−0.1 (−1.3, 1.1)

Dangour et al., Am J Clin Nutr 102:639, 2015

Vitemine im höheren Lebensalter

- Mangel von Vitamin B12 und anderen Vitaminen bei Betagten (> 65 Jahre) prävalent
- Die Datenlage, ob kognitive Veränderungen durch Vitaminsupplementation beeinflusst werden ist aktuell nicht schlüssig
- Bzgl. Der Effekte von Vitaminen auf die Lebensqualität oder den funktionellen Status liegen keine Resultate vor

Summary

Vitamin-B_{12} malabsorption has been found in 21 (30%) of 71 diabetic patients taking long-term metformin therapy in addition to dietary management. The patients with evidence of B_{12} malabsorption had significantly lower haemoglobin levels (and significantly higher serum folic acid levels) than those with normal B_{12} absorption. Steatorrhoea was found in only one patient. Stopping metformin therapy resulted in reversion of B_{12} absorption to normal in most patients examined. Four patients with B_{12} malabsorption were found to have pathologically low serum B_{12} levels. The causes and implications of these findings are discussed and it is concluded that all patients on long-term metformin therapy should have annual serum B_{12} estimations.

Introduction

The biguanides have been used in the treatment of diabetes mellitus since 1957, when they were first reported to have an effective hypoglycaemic action in man (Ungar *et al.*, 1957). Loss of weight has been noted to be one of the effects of this therapy, but the cause is disputed (*Journal of the American Medical Association*, 1970), though intestinal malabsorption is certainly an important factor (Czyzyk *et al.*, 1968; Stowers and Bewsher, 1969). Berchtold *et al.* (1969) reported malabsorption of vitamin B_{12} in patients who had been treated with metformin for two to three months, but their results were not confirmed when other biguanides were used (Willms and Creutzfeldt, 1970).

factor assay was based on the technique of Ardeman and Chanarin (1963). A standard 25-g D-xylose test was used and the results were expressed as a percentage of the dose excreted

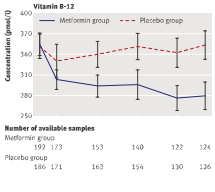
TABLE 1—*Groups of Patients Studied (Mean ± S.E. Mean)*

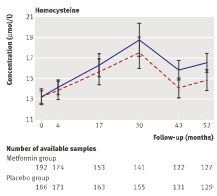
^{57}Co B_{12} Absorption	Age	Daily Hypoglycaemic Dose	Years on Hypoglycaemic Drug	Weight Change (lb.)
		Metformin Patients		
Normal Patients N = 50	61.7 ± 1.36	1.75 ± 0.1 (g Metformin)	4.8 ± 0.3	−3.5 ± 2.6
Abnormal Patients N = 21	63.3 ± 1.95	1.67 ± 0.15 (g Metformin)	4.6 ± 0.37	−6.53 ± 2.68
Significance (Student's *t* test)	$t = 0.64$ $P > 0.05$	$t = 1.6$ $P > 0.05$	$t = 0.42$ $P > 0.05$	$t = 0.66$ $P > 0.05$
		Chlorpropamide Patients		
N = 19	67.4 ± 1.3	502.6 ± 34.25 (mg chlorpropamide)	7.0 ± 0.6*	+5.05 ± 2.6*

*Significantly different from metformin patients (P<0.05).

in five hours. A ^{14}C tripalmitate absorption test was used. This test depends on the excretion of the radioactive carbon in the expired CO_2 after an oral dose of ^{14}C tripalmitate and has been found in this department to be an accurate test of fat absorption (Bhatia *et al.*, 1969).

Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial





De Jager J et al., BMJ 2010;340:c2181

Increased Risk of Cognitive Impairment in Patients With Diabetes Is Associated With Metformin

	Odds-ratio	95% CI	p
Typ 2 DM	1.51	1.03 – 2.21	0.03
Gestörte Glukosetoleranz	0.79	0.34 – 1.85	0.58
Metformin	2.23	1.05 – 4.75	0.04
Metformin, adjustiert für Vitamin B12	1.75	0.81 – 3.78	0.16

Schlussfolgerung der Autoren:
- Metformineinnahme ist mit einem erhöhten Risiko für eine kognitive Dysfunktion assoziiert
- Dies ist teilweise durch den Effekt von Metformin auf den B12-Stoffwechsel erklärt

Morre EM et al., Diabetes Care 36:2981, 2013

Metformin Causing Vitamin B12 Deficiency: A Guilty Verdict Without Sufficient Evidence

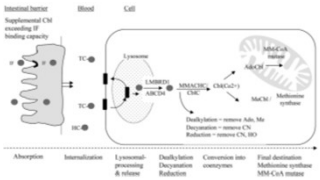
	Vitamin B12	HoloTC	Homo-cystein	MMA
NHANES, 2012	318 vs. 387 pmol/L		9.8 vs. 10.4 mmol/L;	
De Jager, 2010	-19% Risiko für B12 < 150 pmol/l: +7.2% Risiko für B12 150-220 pmol/l: +11.2%		+5%	
Greibe, 2013	↓		→	→
Obeid, 2013	↓	↓	→	→

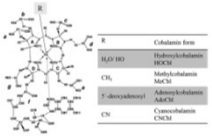
Schlussfolgerung:
- Metformin senkt Vitamin B12, Klinische Bedeutung letztlich unklar
- B12-Messung bei Langzeitmetformintherapie empfohlen

Obeid R, Diabetes Care 37:e22, 2014

Vitamin B12-Substitution:

- i.m. vs. p.o.
- Cyanocobalamin, Hydroxocobalamin, Methylcobalamin, Adenoyslcobalamin

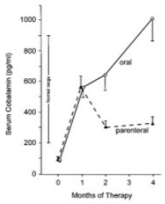


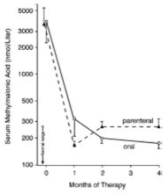


Obeid R et al.,Mol. Nutr. Food Res. 59, 1364, 2015

Effective Treatment of Cobalamin Deficiency With Oral Cobalamin

Cyanocobalamin 1 mg 9 Dosen i.m. vs. 2 mg p.o. tgl.





Kuzminski A et al., Blood 92: 1191, 1998

Vielen Dank