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Design and Methodology of the Trial to Assess Chelation Therapy (TACT):

Design of the Trial to Assess Chelation Therapy

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Abstract

The Trial to Assess Chelation Therapy (TACT) is an NIH-sponsored, randomized, double blind, placebo-controlled, 2×2 factorial clinical trial testing the benefits and risks of 40 infusions of a multi-component Na₂EDTA-chelation solution compared with placebo, and of an oral, high-dose multivitamin and mineral supplement. TACT has randomized and will follow 1708 patients for an average of approximately 4 years. The primary endpoint is a composite of all cause mortality, myocardial infarction, stroke, coronary revascularization, and hospitalization for angina. A 900 patient substudy will examine quality of life outcomes. The trial is designed to have >85% power to detect a 25% relative reduction in the primary endpoint for each treatment factor. Enrollment began in September 2003 and completed in October 2010.

Introduction

National surveys consistently show that over one third of adult patients in the U.S. use alternative therapies^{1,2,3}, for which reliable evidence of net benefits is lacking. Chelation therapy with disodium ethylenediaminetetraacetic acid (Na₂EDTA), a drug currently without indication in the US⁴, is one such therapy.

EDTA chelation of divalent and trivalent ions has been postulated to produce a favorable effect on atherosclerotic plaque, questionably leading to reductions in symptoms, improvement in endothelial function and major vascular events^{5,6,7}. Thus, EDTA chelation is sometimes used for the treatment of coronary and peripheral artery disease, and the disodium salt has been favored because of the potential to decalcify atherosclerotic plaque⁸. There is also ample evidence of potential harm. Disodium EDTA, may cause hypocalcemia and death, particularly when it is infused rapidly⁹. The available evidence for treatment

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effects of chelation therapy in patients with coronary heart disease or peripheral arterial disease is mixed, and limited to case series¹⁰ and three small trials evaluating¹¹¹²¹³ surrogate endpoints.

The ongoing use of a therapy with the potential for benefit as well as harm led to the release of a Request for Applications (RFA 01-004, April 2001) by the National Center for Complementary and Alternative Medicine (NCCAM), co-funded by NCCAM and the National Heart, Lung, and Blood Institute (NHLBI) of the US National Institutes of Health.

METHODS

Design Overview

TACT, ClinicalTrials.gov identifier NCT00044213, is a randomized, double blind, placebo-controlled, 2×2 factorial trial testing the benefits and risks of 40 infusions of a standard multi-component disodium EDTA-chelation solution compared with placebo, and of an oral, high-dose multivitamin and mineral supplement compared with placebo. The primary endpoint is a composite of all cause mortality, myocardial infarction, stroke, coronary revascularization, and hospitalization for angina. This trial is supported by grant number U01 HL92607 from the NHLBI and NCCAM.

The trial uses the components, route, and methods of administration of disodium EDTA chelation recommended by the American College for Advancement in Medicine (ACAM)¹⁴, the largest organization of chelating physicians in North America. The ACAM Board approved the final disodium EDTA dosage and frequency of infusions and all vitamin protocols. The authors are solely responsible for the design and conduct of this study, the drafting and editing of the paper, and its final contents.

Trial Chronology

A grant to conduct the trial was awarded to Mount Sinai Medical Center in August 2002. The US Food and Drug Administration approved the Investigational New Drug application for the Akzo Nobel (Lima, OH, USA) formulation of disodium EDTA chelation in April 2003 (IND # 66,743). The first patient was randomized in September 2003. The trial concluded enrollment of 1708 patients in October 2010. The last TACT follow-up visit will take place in October 2011.

Trial Administration

The Clinical Coordinating Center (CCC) is located at Mount Sinai Medical Center, Miami Beach FL. The Duke Clinical Research Institute (Durham, NC) serves as the Data Coordinating Center (DCC), and the Economics and Quality of Life Coordinating Center. The TACT central pharmacy (Accu-Care Services Pharmacy, Miami FL 9/10/2003 TO 6/18/2010, and Universal Arts Pharmacy from 6/28/2010 to the present) has mixed and delivered, to date, over 50,000 bags of blinded chelation solution and the corresponding oral vitamin supplements to clinical sites.

Clinical sites

Clinical sites complete TACT investigator and coordinator training. They meet all NIH, FDA, and Office for Human Research Protections requirements for participation in federally-funded studies.

Data collection

TACT data collection takes place through an Internet-based, electronic data capture system (TrialMaster™, OmniComm Systems, Davie FL). This permits real-time, patient-specific prescription of the EDTA dose of the active chelation solution, based on an individual patient's estimated glomerular filtration rate (eGFR). An unblinded physician not otherwise involved with the study at the CCC gives patient-specific prescription approval.

Specific steps with regards to training, site visits by the DCC, and TrialMaster programming are taken to assure the integrity of the patient data collected in TACT.

Patient safety oversight and adverse event

The NIH, FDA, and local or central IRBs oversee TACT. A Data and Safety Monitoring Board (DSMB) reviews unblinded outcome and safety data approximately every 6 months, and recommends whether to continue the trial. The members of the DSMB include experts in clinical trial design and interpretation, bioethics, cardiology, pharmacology, chelation therapy, and biostatistics.

The site investigator documents all adverse events and serious adverse events (SAE) that occur from initiation of study drug through 30 days following the final study infusion. The site investigator assigns causality to each SAE. The DCC Medical Monitor or designee determines which SAEs meet the "unexpected" criteria (not labeled in the Investigator's Brochure) and makes an independent assessment of causality. A blinded Clinical Events Committee performs clinical event adjudication.

Patient population

Patients are eligible if they are at least 50 years of age and have had an acute myocardial infarction more than 6 weeks prior to enrollment, and are ineligible if they have abnormal renal function or other exclusions (Tables I and II).

Randomization

Randomization is carried out on the TACT TrialMaster™ System. Patients are randomly assigned in equal proportions to one of the four treatment arms defined by the 2×2 factorial design.

Treatment regimens

All eligible consenting patients are randomized to receive 40 infusions of either chelation solution (Table III) or placebo, consisting of 500 mL of normal saline and 1.2% dextrose. The first 30 infusions occur weekly. The final 10 infusions may occur between 2 weeks and up to 8 weeks apart. Each patient is also randomized to receive either an oral high-dose vitamin and mineral supplement, or identical-appearing placebo pills (Table IV). The dosing and components of the high-dose oral vitamins were developed with the collaboration of ACAM and represent the typical multi-intervention treatment offered by chelation therapy practitioners. Finally, during the infusion phase of the trial, all study patients receive a daily low-dose regimen consisting of vitamin B6 25 mg, zinc 25 mg, copper 2 mg, manganese 15 mg, and chromium 50 mcg, to prevent depletion by the chelation regimen.

Blinding

The chelation solution is blinded using a previously piloted method¹⁵. The shipped and refrigerated infusion pack contains an ascorbic acid syringe (or ascorbic acid placebo), one syringe with EDTA (or EDTA placebo), and a bag for intravenous infusion with all the other components already mixed (or a bag containing only normal saline if the patient is assigned

to the placebo arm). At the time of infusion, the Site Coordinator injects the contents of the syringe into the infusion bag. The placebo oral high-dose vitamins are identical-appearing to the active therapy.

Patient follow-up

Patients are seen at baseline, and at each of the 40 infusion visits. Following the infusion phase of the trial, patients are contacted quarterly by telephone, have annual clinic visits, and are seen at the end of the trial or at the 5 year followup, whichever occurs first. TACT study procedures recommend evidence-based concomitant care for post-MI patients.

Safety monitoring

The most important potential adverse events are hypocalcemia and renal toxicity. Nephrotoxicity has been encountered with far higher doses than TACT uses as well as more frequent administration¹⁶¹⁷, and in patients with underlying renal disease. Patients with a baseline creatinine >2.0 are excluded from the trial. Renal function is assessed at baseline, and 9 additional times during the infusion regimen. Sites are issued an electronic alert, copied to the CCC, when there is a 25% decrease in estimated GFR, and infusions stop until creatinine levels return to baseline. Infusions are permanently stopped when there is either a doubling of serum creatinine, or an increase to a level of 2.5 mg/dL, whichever is lower. Hematuria and proteinuria are assessed using urine dipstick.

Hypocalcemia due to rapid administration of disodium EDTA is another potentially serious side effect⁸. Patients receive infusions over a three-hour period and over a longer time-span if the calcium level, corrected for albumin concentration, is low. Short infusions are reported electronically to the site, the CCC, and the DCC.

Hypoglycemia in diabetics is another potential side effect. Diabetics on insulin snack before the infusion, and sites are able to treat hypoglycemia if necessary.

Additional side effects include hypotension, trace metal and vitamin deficiency syndromes, febrile episodes, and heart failure due to fluid overload. During the trial, the patient consent and brochure were modified to include heart failure as a possible adverse event associated with the infusions. The FDA was notified of this finding. The trial also instituted weighing patients prior to all infusions and required a clinical evaluation if the patient had gained 5 lbs or more since the baseline visit to rule out potential progression or new onset of heart failure.

Infusions are delayed in patients whose ALT, AST, alkaline phosphatase or bilirubin double, or total white blood cell count falls below the normal limit. The development of thrombocytopenia to below 100,000 platelets, or a 50% decrease from baseline leads to a delay of infusions until platelet count reverts to normal levels, and an omission of unfractionated heparin from future infusions.

All SAEs are reported to the Data and Safety Monitoring Board, NIH, and FDA on a regular basis. Deaths and unexpected SAEs are reported in an expedited fashion to the above and to the IRBs. Hospitalizations for heart failure are reported to the DSMB and NIH in an expedited fashion.

Study endpoints

The primary endpoint is a composite of all cause mortality, myocardial infarction, stroke, coronary revascularization, and hospitalization for angina. A key secondary endpoint is the composite of cardiovascular death, non-fatal MI, or non-fatal stroke.

There are 4 other pre-specified secondary endpoints: 1] quality of life; 2] cost-effectiveness of therapy, 3] high sensitivity C-reactive protein, and 4] estimated GFR.

Baseline quality of life data includes eight scales from the Medical Outcomes Study Short Form (SF-36)¹⁸, the Duke Activity Status Index (DASI)¹⁹, bed and disability day questions from the National Interview Survey²⁰, job class and days lost from work and the Seattle Angina Questionnaire²¹, the New York Heart Association congestive heart failure class and the Canadian Cardiovascular Society class for angina. The EuroQol²² utility is collected at baseline. A random subset of 900 patients undergoes telephone interviews at 6, 12, and 24 months follow-up. Economic analyses comparing costs between arms will be conducted if either of the experimental therapies demonstrates a reduction in the primary endpoint. The level of C-reactive protein will be compared between treatment groups in 600 patients. We will compare estimated GFR in patients receiving active EDTA treatment compared with those receiving placebo infusions.

Clinical CVD Event rates and statistical power

TACT originally planned to enroll 2372 patients over 3 years. Difficulties in enrolling the requisite numbers of patients ultimately led to a reduction in the total sample size to 1700 patients, with a counterbalancing extension in median followup to 4 years. The event rates in each control arm of TACT were estimated based on published data on similar post-MI patient populations participating in clinical trials²³, namely 20% or higher after 2.5 years of followup. The level of non-compliance with EDTA (or placebo) infusion therapy and oral vitamin (or placebo) expected in TACT was estimated as 7.2% of patients per year, or 22% over 3 years. We also assumed a loss to follow-up rate of up to 3% of patients in the trial. This statistical plan provides 85% power for detecting a 25% relative reduction in the primary endpoint for each treatment.

Statistical analysis

All major treatment comparisons will be performed according to the principle of intention-to-treat. Statistical comparisons will be performed using two-sided significance tests. The primary statistical assessments will compare EDTA chelation with placebo infusions, and oral high-dose vitamins with oral placebo. The log-rank test²⁴ will be used for the adjusted comparisons of each treatment factor. Cumulative event rates will be calculated according to the Kaplan-Meier method²⁵. Hazard ratios with associated confidence intervals will be derived from the Cox proportional hazards model²⁶. The Cox model will also be used to assess whether there is an interaction of EDTA chelation therapy with high dose vitamins. Interim treatment comparisons are monitored with the use of 2-sided, symmetric O'Brien-Fleming boundaries generated with the Lan-DeMets alpha-spending function approach to group-sequential testing^{27,28}.

Subgroup analyses

A limited number of pre-specified subgroup analyses of the primary outcome and selected secondary outcomes will test the efficacy of chelation therapy and/or high dose vitamins. Treatment comparisons will be performed within subgroups defined by:

1. Age >70 years versus younger patients;
2. Gender;
3. Race;
4. MI location;
5. Time from index MI to trial enrollment;

6. Diabetes and metabolic syndrome;
7. Patients in whom statin therapy is not being used;
8. Patients at risk to have had exposure to lead during their lifetime;
9. Patients who have received 80% of assigned therapy, whether infusions or oral high-dose vitamin therapies;
10. Patients who have received at least one infusion as assigned.

Subgroup differences in treatment effects will be assessed with the Cox model, by testing for interactions between the randomized treatment factor and the specific baseline variables listed above.

Discussion

National surveys have documented widespread use of CAM by patients across a broad spectrum of diagnoses¹². ACAM, and other organizations trains chelation practitioners annually. The Centers for Disease Control and Prevention estimate that approximately 111,000 US adults used chelation therapy in 2007³, a 66% increase since the previous survey in 2002²⁹. The need to accumulate sufficient randomized evidence of a CAM therapy such as EDTA chelation goes beyond the need to identify a new therapy for patients with coronary disease. The labeled toxicities, which include renal insufficiency, cardiac arrhythmias, hypocalcemia, hematologic problems, respiratory arrest, and death, must be assessed in the context of a therapy with potential, but unproven benefits. This fair and balanced assessment can be carried out only in the context of a randomized trial.

The interpretation of any benefit or harm of chelation therapy as used in the community would be confounded by the concomitant use of high-dose oral supplements, a common clinical practice. Moreover, the use of high-dose supplements may not be innocuous³⁰³¹³². Thus, the vitamin-treatment comparison, like the chelation comparison, stands alone as important for the assessment of efficacy, as well as safety.

Besides challenges typical of large multisite trials, TACT was faced with several additional hurdles. Substantial recruitment difficulties led NIH to organize a review of trial progress carried out by a panel of experts in cardiovascular research independent of NIH, of the trial DSMB, and of trial investigators. Despite estimates that trial completion would be delayed several years, this independent committee concluded TACT should continue with a reduced sample size. Concerns about the informed consent process, and about trial conduct at several clinical sites also prompted investigations by OHRP and FDA respectively. Following their reviews, each Federal agency recommended the trial could continue after corrective steps were taken. All sites met NIH, FDA, and Office for Human Research Protections requirements for participation in federally-funded studies, including ethics review by a local or central IRB with a Federal-Wide Assurance. Details on these implementation issues will be presented in a subsequent article.

At this time TACT has finished enrollment, has delivered the final infusions and vitamins, and is expected to present final results in 2012.

Conclusions

TACT has been designed to test whether EDTA chelation therapy and high-dose oral vitamin and mineral therapy offer clinical, quality of life, and economic benefits for patients with a prior MI.

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References

1. Eisenberg DM, Kessler RC, Foster C, et al. Unconventional Medicine in the United States: Prevalence, Costs, and Pattern of Use. *N Engl J Med*. 1993; 328:246–252. [PubMed: 8418405]
2. Barnes PM, Powell-Griner E, McFann K, et al. Complementary and alternative medicine use among adults: United States 2002. *Adv Data*. 2004; 343:1–19. [PubMed: 15188733]
3. Barnes PM, Bloom B, Nahin R. Complementary and alternative medicine use among adults and children: United States, 2007*. *National Health Statistics Reports*; no 12. National Center for Health Statistics. 2008; 12:1–24.
4. U.S. Department of Health and Human Services. Food and Drug Administration. Public Health Advisory: Edetate Disodium. (marketed as Endrate and generic products). [Updated: 08/09/2010;cited 2010 Nov 16]. Available from: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051138.htm>
5. Olszewer E, Carter JP. EDTA chelation therapy in chronic degenerative disease. *Med Hypotheses*. 1988; 27(1):41–9. [PubMed: 3144646]
6. Ernst E. Chelation therapy for coronary heart disease: An overview of all clinical investigations. *Am Heart J*. 2000; 140(1):139–141. [PubMed: 10874275]
7. Green DJ, O'Driscoll JG, Maiorana A, et al. Effects of chelation with EDTA and vitamin B therapy on nitric oxide-related endothelial vasodilator function. *Clin Exp Pharmacol Physiol*. 1999; 26:853–856. [PubMed: 10561804]
8. Bolick LE, Blakenhorn DH. A quantitative study of coronary artery calcification. *Am J Path*. 1961; 39:511. [PubMed: 13870788]
9. U.S. Centers for Disease Control. Deaths Associated with Hypocalcemia from Chelation Therapy --- Texas, Pennsylvania, and Oregon, 2003—2005; Morbidity and Mortality Weekly Report(MMWR). 2006. p. 204-207.[Updated: 3/2/2006; cited 2010 Nov 16]. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5508a3.htm>
10. Grier MT, Meyers DG. So much writing, so little science: A review of 37 years of literature on Edetate Sodium chelation therapy. *Ann Pharmacother*. 1993; 27:1504–1509. [PubMed: 8305786]
11. Guldager B, Jørgensen R, Jørgensen SJ, et al. EDTA treatment of intermittent claudication-a double-blind, placebo-controlled study. *J Intern Med*. 1992; 231(3):261–7. [PubMed: 1556523]
12. Van Rij AM, Solomon C, Packer SG, et al. Chelation therapy for intermittent claudication. A double-blind, randomized, controlled trial. *Circulation*. 1994; 90(3):1194–1199. [PubMed: 8087928]
13. Knudtson ML, Wyse DG, Galbraith PD, et al. Chelation therapy for ischemic heart disease: a randomized controlled trial. *J Am Med Assoc*. 2002; 287(4):481–486.
14. Rozema TC. Special Issue: Protocols for chelation therapy. *J Adv Med*. 1997; 10(1):5–90.
15. Lamas GA, Ackermann A, Hollar D, et al. Chelation therapy for patient with coronary heart disease: Findings from the pilot to Assess Chelation Therapy. *J Am Coll Cardiol*. 2004; 43:252A.
16. Holland JF, Danielson E, Sahagian-Edwards A. Use of ethylene diamine tetra acetic acid in hypercalcemic patients. *Proc Soc Exper Biol Med*. 1953; 84:359–364. [PubMed: 13121040]

17. Foreman H, Finnegan C, Lushbaugh CC. Nephrotoxic hazard from uncontrolled edathamil calcium-disodium therapy. *JAMA*. 1956; 160:1042–1046.
18. Ware, JE., Jr; Snow, KK.; Kosinski, M., et al. SF-36 Health Survey: Manual & Interpretation Guide. Nimrod Press; Boston: 1993.
19. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol*. 1989; 64(10):651–654. [PubMed: 2782256]
20. National Center for Health Statistics. Health, United States, 1991. Public Health Service; Hyattsville, Maryland: 1992.
21. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995; 25(2):333–341. [PubMed: 7829785]
22. EuroQol Group. A new facility for the measurement of health related quality of life. *Health Policy*. 1990; 16:199–208. [PubMed: 10109801]
23. O'Connor CM, Dunne MW, Pfeffer MA, et al. Azithromycin for the Secondary Prevention of Coronary Heart Disease Events. *J Am Med Assoc*. 2003; 290(11):1459–1466.
24. Kalbfleisch, JD.; Prentice, RL. *The Statistical Analysis of Failure Time Data*. Second Edition. John Wiley & Sons, Inc; New York: 2002.
25. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Statist Assn*. 1958; 53:457–481.
26. Cox DR. Regression models and life-tables (with discussion). *J Royal Statist Soc B*. 1972; 34:187–220.
27. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979; 35:549–556. [PubMed: 497341]
28. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983; 70:659–663.
29. Nahin RL, Barnes PM, Stussman BJ, et al. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. *Natl Health Stat Report*. 2009; (18):1–14. [PubMed: 19771719]
30. Brown BG, Zhao X-Q, Chait A, et al. Simvastatin and Niacin, Antioxidant Vitamins, or the Combination for the Prevention of Coronary Disease. *N Engl J Med*. 2001; 345:1583–1592. [PubMed: 11757504]
31. Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005; 142(1):37–46. [PubMed: 15537682]
32. Vivekananthan DP, Penn MS, Sapp SK, et al. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet*. 2003; 361:2017–23. [PubMed: 12814711]

Inclusion Criteria**Table I**

All of the following inclusion criteria must be present.

1. Men or post-menopausal women age 50 years or older
 2. Myocardial infarction (MI) over 6 weeks prior to evaluation, defined by criteria A, B, or C:
 - A. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of cardiac biomarkers with at least one of the following:
 - 1) Ischemic symptoms;
 - 2) Pathologic Q waves; or
 - 3) ECG changes of ischemia;
 - or
 - B. Imaging evidence of myocardial scar, and angiographic evidence of coronary disease in that distribution,
 - or
 - C. Past ischemic symptoms, MI on ECG, and segmental wall motion abnormality or scar on an imaging study, with review and agreement by the CCC.
-

Exclusion Criteria**Table II**

None of the following exclusion criteria may be present.

- Chelation therapy within 5 years.
 - Allergy to any study drug.
 - Coronary or carotid revascularization within 6 months.
 - Planned revascularization.
 - Symptomatic or clinically evident heart failure.
 - Heart failure hospitalization within 6 months.
 - Blood pressure >160/100
 - No venous access.
 - Serum creatinine >2.0 mg/dl.
 - Platelet count <100,000/mm
 - Cigarette smoking within the last 3 months.
 - Liver disease, or ALT or AST > 2.0 times the upper limit of normal.
 - Diseases of copper, iron, or calcium metabolism.
 - Inability to tolerate 500cc of fluids weekly.
 - Inability to keep to study schedules.
 - Medical condition likely to affect patient survival within 4 years.
 - Women of child-bearing potential.
-

Table III
Chelation Infusion Contents

Additive
Up to 3 grams of disodium EDTA
2 grams of magnesium chloride
100 mg of procaine HCL
2500 units of heparin
7 grams of ascorbate
2 mEq KCl
840 mg sodium bicarbonate
250mg pantothenic acid
100mg of thiamine
100mg of pyridoxine
QS with sterile water to 500ml

The dose of EDTA changes on estimated GFR; the maximum dose is 3 grams.

Table IV
High Dose Oral Contents

High Dose Regimen (Taken Twice Daily)	Total Amount for 6 Pills	% RDA
Vitamin A	25,000	IU 500%
Vitamin C	1,200 mg	2000%
Vitamin D ₃	100 IU	25%
Vitamin E	400 IU	1333%
Vitamin K1	60 mcg	75%
Thiamin	100 mg	6667%
Niacin	200 mg	1000%
Vitamin B ₆	50 mg	2500%
Folate	800 mcg	200%
Vitamin B ₁₂	100 mcg	1667%
Biotin	300 mcg	100%
Pantothenic acid	400 mg	4000%
Calcium	500 mg	50%
Iodine	150 mcg	100%
Magnesium	500 mg	125%
Zinc	20 mg	133%
Selenium	200 mcg	286%
Copper	2 mg	100%
Manganese	20 mg	400%
Chromium	200 mcg	167%
Molybdenum	150 mcg	200%
Potassium	99 mg	3%
Choline	150 mg	*
Inositol	50 mg	*
PABA	50 mg	*
Boron	2 mg	*
Vanadium	39 mcg	*
Citrus Bioflavonoids	100 mg	*

RDA = recommended daily allowance

* = RDA not established Other ingredients: Croscarmellose sodium, microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose, silicon dioxide.