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Cleveland Clinic Clinical Rx Forum

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Labeling Changes for Dietary Supplements

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Introduction: In 2016 the Food and Drug Administration (FDA) published a final rule regarding a change in dosage labeling of vitamins A, D, E, folic acid, and niacin.[1,2] Rather than being dosed in International Units (IU), vitamins D and E will be converted to more accurate measures of micrograms (mcg) and milligrams (mg), respectively.[3] Vitamin A dosage forms labeled as IU will be converted to mcg of retinol activity equivalents (RAE). Folic acid (synthetic form of vitamin B9) will now be listed as folate (naturally-occurring). Instead of being measured in mg, folic acid will be measured in mcg of dietary folate equivalents (DFEs). Niacin (vitamin B3), formerly listed as mg, will now be listed as mg of niacin equivalents (NE).[4] These label changes only apply to over-the-counter dietary supplements and not to prescription products.[5] These updates to the labeling are accompanied by modifications to serving size, percent daily value, and suggested use to help the consumer make educated choices regarding nutrition and supplementation.[3]

Rationale for New Labeling: The new dosage labeling for dietary supplements occurred due to two factors: 1) evolution of the American diet and 2) advancements in nutrition science.[3] Some of the supplements are being converted to account for differing bioactivities.[6] For example, the Vitamin A conversion includes other related pro-vitamins such as beta-carotene, and therefore, more accurately depicts its biologic activity. The DFE designation accounts for synthetic folic acid and naturally-occurring forms of folate.[7] Additionally, the NE dosage calculation takes into consideration the conversion of tryptophan to niacin; supplements with tryptophan and niacin have a higher NE designation than those without tryptophan.[8] In regards to vitamin D dosage conversion from IU to mcg, it is important to note that all forms of vitamin D (e.g., vitamin D [ergocalciferol + cholecalciferol], vitamin D2 [ergocalciferol], and vitamin D3 [cholecalciferol]) utilize the same conversion factor.[7]

Dosage Conversions: Examples of common dose conversions for supplements are listed below.[7,9]

- Vitamin D: 1000 IU = 25 mcg
- Vitamin E: 35 IU = ~16 mg
- Vitamin A: 3500 IU = 1050 mcg RAE
- Folic Acid 400 mcg = ~600 mcg DFE
- Niacin 1 mg = 1 mg NE (supplement without tryptophan)

Reducing Confusion: The Institute for Safe Medication Practices (ISMP) has advocated for the FDA to include either mcg or mg, respectively, as well as IU on some supplements to help reduce confusion.[2] In regards to vitamin D, the FDA has agreed to let manufacturers voluntarily maintain dosage in IU as long as the dosage is first listed in mcg with IU followed in parentheses.[10] This is meant to help avoid confusion and smoothen the transition to the new labeling. Folate products will also fol-

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low in a similar suit.[11] Manufacturers may voluntarily include quantitative amounts of naturally-occurring folate in mcg DFE on conventional food labels. However the designation of mcg DFE followed by mcg of folic acid in parentheses is mandatory if a claim is made about the product or if synthetic folic acid is added.[9,11] The transition to either mcg or mg may help alleviate dosing errors associated with the use of the IU abbreviation that is sometimes confused with either "10" (ten) or "IV" (intravenous).[5]

Considerations for Pharmacists: As these labeling changes are in the process of being implemented, there will be significant room for dosing errors.[5] Providers may not be aware of the update to the new units of measure in which these supplements are now being dosed. Pharmacists will need to educate patients regarding these labeling changes. Since some of the vitamins affected are fat soluble (A, D, and E), it is important to be mindful of dosing errors as accumulation may be of concern. Toxicities of these vitamins can include, but are not limited to: headache, nausea, vomiting, lethargy, confusion, weakness, hepatotoxicity, and arrhythmia.[12-15] Assuring that patients are prescribed and are using the recommended amount of these supplements is imperative for quality patient care and safety.[9] For example, the new recommendation for folic acid supplementation for pregnancy is at least 600 mcg/day DFE from prenatal vitamins and diet, this is the conversion from the minimum of 400 mcg/day of folic acid. Tolerable daily upper intake levels of these supplements in adults are as follows[16,17]**:**

- Vitamin D: 100 mcg (4000 IU)
- Vitamin E: 1000 mg (1500 IU)
- Vitamin A: 3000 mcg RAE (3000 mcg retinol)
- Folate: 1000 mcg DFE (500 mcg folic acid)
- Niacin: 35 mg NE (35 mg)

When will these changes be in full effect? Currently, some manufacturers have already introduced the new labeling.[3] However, compliance dates listed below are based on the date that the labels are affixed to the bottles, so old labeling may appear for some time after these deadlines[1]:

Manufacturers with **$10 million or more** in annual sales: By January 1, 2020

Manufacturers with **less than $10 million** in annual sales: By January 2021

How will these labeling changes be implemented in Epic? Dose conversions will appear within ordering instructions as well as product-specific administration instructions for impacted agents within Epic.

References:

1. U.S. Food and Drug Administration. [Internet]. FDA In Brief; 2018. Available from: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-issues-final-rule-extend-compliance-date-updated-nutrition-facts-label-and-serving. Accessed: Aug 2019.
2. Institute for Safe Medication Practices. (2019). Container label changes for vitamin A, D, and E. [online] Available from: https://www.ismp.org/resources/container-label-changes-vitamin-d-and-e Accessed: Sept 2019.
3. Be Label Wise. [Internet] A Guide to Understanding Supplement Facts. Available from: https://belabelwise.org/fact-sheet/. Accessed: Aug 2019.
4. Office of Dietary Supplements - Niacin. NIH Office of Dietary Supplements. Available from: https://ods.od.nih.gov/factsheets/Niacin-HealthProfessional/. Accessed: Sept 2019.
5. Watch for New Units on Some Vitamin and Supplement Labels. Pharmacist's Letter. Available from: https://pharmacist.therapeuticresearch.com/Content/Articles/PL/2019/Feb/Watch-for-New-Units-on-Some-Vitamin-and-Supplement-Labels. Accessed: Sept 2019.
6. National Institutes of Health [Internet]. Vitamin A; 2019. Available from: https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/. Accessed: Sept 2019.
7. Fda.gov. (2019). Converting Units of Measure for Folate, Niacin, and Vitamins A, D, and E on the Nutrition and Supplement Facts Labels: Guidance for Industry. Available from: https://www.fda.gov/media/129863/download. Accessed: Sept 2019.
8. Fukuwatari T, Shibata K. Nutritional aspect of tryptophan metabolism. Int J Tryptophan Res. 2013;6(Suppl 1):3–8.
9. Clinical Resource, Dietary Supplement Labeling Changes: A Dose Conversion Chart. Pharmacist's Letter/Prescriber's Letter. Feb 2019.
10. Food Labeling: Revision of the Nutrition and Supplement Facts Labels. Federal Register. Available from: https://www.federalregister.gov/documents/2016/05/27/2016-11867/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels. Published May 27, 2016. Accessed: Aug 2019.
11. Food Labeling; Revision of the Nutrition and Supplement Facts Labels; Technical Amendments. Federal Register. Available from: https://www.federalregister.gov/documents/2018/12/21/2018-27431/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels-technical-amendments. Published December 21, 2018. Accessed: Aug 2019.
12. Lexi-Tox [Internet]. Vitamin A; 2019. Available from: http://www.crlonline.com/lco/action/doc/retrieve/docid/lexier/1302239?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dvitamin%2520a%26t%3Dname%26va%3Dvitamin%2520a. Accessed Sept 2019.
13. Lexi-Tox [Internet]. Vitamin D; 2019. Available from: http://www.crlonline.com/lco/action/doc/retrieve/docid/lexier/1299999?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dvitamin%2520d%26t%3Dname%26va%3Dvitamin%2520d. Accessed: Sept 2019.
14. Lexi-Tox [Internet]. Vitamin E; 2019. Available from: http://www.crlonline.com/lco/action/doc/retrieve/docid/lexier/6200127?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dvitamin%2520e%26t%3Dname%26va%3Dvitamin%2520e. Accessed: Sept 2019.
15. Lexi-Tox [Internet]. Niacin; 2019. Available from: http://www.crlonline.com/lco/action/doc/retrieve/docid/lexier/1322599?searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dniacin%26t%3Dname%26va%3Dniacin. Accessed: Sept 2019.
16. National Academy of Sciences. Dietary Reference Intakes Tables and Application. Available from: http://nationalacademies.org/hmd/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx. Published September 6, 2019. Accessed: Sept 2019.
17. Vitamin E. NIH Office of Dietary Supplements. Available from: https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/?print=1 Accessed: Sept 2019.

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Brolucizumab (Beovu®)	Monoclonal Antibody	Neovascular (wet) Age-related Macular Degeneration	Restricted to Ophthalmology for outpatient use only
Carbidopa/Levodopa Extended-Release Capsule (Rytary®)	Anti-Parkinson Agent	Parkinson's Disease	Restricted to continuation of therapy
Tacrolimus Extended-Release Tablet (Envarsus XR®)	Calcineurin Inhibitor	Immunosuppression after Organ Transplant	Restricted to Transplant Service

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Anakinra (Kineret®)	Interleukin-1 Receptor Antagonist	Pericarditis	Modify restriction to include: Cardiothoracic Surgery and Cardiology for continuation of therapy for recurrent pericarditis in patients with contraindications or failure to standard therapies (e.g., colchicine, NSAIDs, and corticosteroids). Initiation of therapy is restricted to Cardiology.
Cangrelor (Kengreal®)	Antiplatelet Agent	Bridging Therapy	Modify restriction to include: Cardiology consult required to be used as bridging therapy when there is need for rapid reversal of antiplatelet (within an hour). There should be consideration for timing since stent was placed, duration of IV antiplatelet therapy, and initiation of oral therapy as soon as possible.
Darbepoetin alfa (Aranesp®)	Colony Stimulating Factor	Anemia	Standardize restriction to state: For inpatients with ESRD or CKD defer darbepoetin alfa administration until hospital day 7 unless the hemoglobin is < 8 g/dL. Pharmacists may automatically: 1) retime darbepoetin alfa if ordered earlier than day 7 in these patients 2) round to nearest vial/syringe size. Pharmacists will contact provider if hemoglobin is > 11 g/dL to recommend discontinuation of darbepoetin alfa. Hem/Onc indications for darbepoetin alfa use are excluded from this restriction criteria. This restriction is for Ohio hospitals only.

NSAID=Nonsteroidal Anti-inflammatory Drug IV=Intravenous ESRD= End Stage Renal Disease CKD=Chronic Kidney Disease Hem/Onc=Hematology/Oncology

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Digoxin Immune Fab (DigiFab®)	Antidote	Digoxin Toxicity	Prescribing/Dosing Guidelines:* 1) Bradycardia (HR < 50 bpm) with hemodynamic instability/hypotension (SBP<90) with: a) failure of atropine 1 mg IV push x 3 doses b) contraindication or inability of patient to be paced and c) exclusion of other causes of bradycardia (correction of hyperkalemia, nodal blocking agents) 2) Life-threatening ventricular dysrhythmias 3) Dosing Guidelines: a) Round dose up to next nearest vial size b) No repeat doses (exception is an intentional overdose) and c) Do not draw digoxin levels after administration of digoxin immune Fab
Eculizumab (Soliris®)	Monoclonal Antibody	NMOSD	Modify restriction to include: NMOSD in the outpatient setting
Epinephrine 100 mcg/10 mL Bolus Syringes	Alpha/Beta Agonist	Vasopressor	Modify restriction to state: Epinephrine 100 mcg/10 mL IV Bolus Syringes are restricted for use by ED Staff Physicians at patient bedside for medication administration
Ferric Carboxymaltose (Injectafer®)	Iron Preparation	Iron Deficiency	Modify restriction to include: Use by Nephrology in non-dialysis dependent CKD patients in the outpatient setting
Four-Factor Prothrombin Complex Concentrate (Kcentra®)	Blood Factor	Coagulopathy	Modify restriction to include: One-time dose according to the dosing table for correction of coagulopathy in patients with acute liver failure prior to ICP monitor placement†

*Note: These are not formal restrictions, but guidance for appropriate use. See additional dosing guidance in Lexicomp.
†Dosing table will be available in Lexicomp and in the Restricted Drug List on the Drug Information SharePoint Site
HR=Heart Rate SBP=Systolic Blood Pressure NMOSD=Neuromyelitis Optica Spectrum Disorder IV=Intravenous
ED=Emergency Department CKD=Chronic Kidney Disease ICP=Intracranial Pressure

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions/ Comments**
Ketamine	General Anesthetic	Severe Agitation Pain	Restriction modified for use by: **Inpatient:** **1)** Emergency Medicine Staff physicians per guidelines and protocols and **Critical Care Transport NPs for severe agitation and sub-dissociative dosing** 2) ICUs 3) Acute Pain Management Service (See Adult IV Guidelines for non-ICU units meeting the monitoring parameters in the Subanesthetic Ketamine Infusion SOP) **Outpatient:** 1) Psychiatry and Chronic Pain Management
Ustekinumab (Stelara®)	Monoclonal Antibody	UC	Modify restriction to include: Use by Gastroenterology as second-line therapy in UC patients in the outpatient setting

NP=Nurse Practitioner ICU= Intensive Care Unit SOP=Standard of Practice UC= Ulcerative Colitis

Conversions and Line Extension to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Conversion**
Itraconazole Oral Solution (Sporanox®)	Antifungal Agent	Fungal Infections	Approval was granted for conversion to generic itraconazole oral solution.
Sirolimus Oral Solution (Rapamune®)	Immunosuppressant Agent	Prevention of Organ Transplant Rejection	Approval was granted for conversion to generic sirolimus oral solution
Rivaroxaban (Xarelto®)	Direct Oral Anticoagulant	Prevention of CV outcomes in CAD and PAD	The 2.5 mg tablet of rivaroxaban was added as a line extension

CV=Cardiovascular CAD=Coronary Artery Disease PAD=Peripheral Arterial Disease

Therapeutic Interchanges on Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange**
Mixed Insulin Products	Insulin	Diabetes	Mixed Insulin Products will be converted to the equivalent dose of Humulin® 70/30 N/R insulin
Mixed Insulin Analog Products (Humalog® 75/25, Novolog® 70/30)	Insulin	Diabetes	Mixed Insulin Analog Products (Humalog® 75/25 and Novolog® 70/30) will be converted to the equivalent dose of Humulin® 70/30 N/R insulin
Humalog® 50/50	Insulin	Diabetes	Humulin® 50/50 will be converted to the equivalent dose of N/R insulins

N/R=NPH/Regular

Denial to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comment**
Tafamidis Capsules (Vyndamax™ and Vyndaqel®)	Transthyretin Stabilizer	Amyloid Cardiomyopathy	Patients will be allowed to use own supply

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Infliximab-dyyb (Inflectra®)	Monoclonal Antibody	CD UC	Restricted to outpatients ≥ 6 years of age with CD or UC whose insurance mandates the use of Inflectra®
Mepolizumab (Nucala®)	Monoclonal Antibody	Eosinophilic Asthma	Restricted to the Departments of Pediatric Allergy and Clinical Immunology and Pediatric Pulmonary Medicine for use in the outpatient setting only

CD=Crohn's Disease UC=Ulcerative Colitis

Change to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes**
Tacrolimus Suspension	Calcineurin Inhibitor	Immunosuppression	Tacrolimus suspension concentration will be changed from 0.5 mg/mL to 1 mg/mL