FDA U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR FOOD SAFETY & APPLIED NUTRITION

FDA Regulation of Color Additives in Drug Products

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Learning Objectives

- Recognize a color additive
- Describe color additive petition process
- Identify certification exempt color additives
- Identify certified color additives
- Summarize certification process for color additives
- Identify enforcement tools

Definition of Color Additive

- A color additive is a substance that imparts color to a food, drug, cosmetic, or medical device
- FDA has regulatory responsibilities for all of these products when they are marketed in the U.S.
- FDA must pre-approve the color additives used in FDA-regulated products

Ideal Properties of Color Additives

- Non-toxic and no physiological activity
- High coloring power so only small quantity needed
- Stable
  - Not light sensitive
  - Not temperature sensitive
  - pH stable
- Free from taste or odor
- Water or oil soluble depending on formulation

Types of Color Additives

- Dyes and pigments
- Inorganic and mineral compounds
- Plant and animal sources
- Lakes – insoluble pigments formed from water-soluble dyes, precipitants, and substrata
- Mixtures – color additives made by mixing multiple color additives and one or more diluents
  - Diluents facilitate the use of mixtures in products
  - Listed for drug use under 21 CFR 73.1001
    - Injected drugs
    - Branding inks
    - Externally applied drugs

Permitted Uses for Color Additives in Drugs

- General use
  - Ingested drugs
- External use
  - Topically applied drugs
- Specific products
  - Mouthwashes and dentifrices
- Eye area use
  - Must be specifically authorized

Purposes of Drug Coloring

- Drug recognition
  - Different colors for different pills
- Branding
  - Purple pills
  - Blue pills

- Psychological effects
  - Calm blue for good night's sleep
  - Bright red for speedy recovery
- Brighter colors for children's medicines
- Uniform colors for standard preparations
  - Natural calamine - colored with red iron oxide
  - Lactose used as diluent – colored with caramel

- Opacity for light-sensitive products
  - Keeps active ingredients stable
    - e.g., iron oxides, titanium dioxide, aluminum lakes

Types of Drug Coloring

- Tablets
  - Inner core
  - Outer coating
- Hard or soft gelatin capsules
  - Outer shell
  - Coated beads
- Oral liquids
- Topical creams
- Toothpastes, mouthwash
- Ointments

Color Additive Requirements in Federal Food, Drug, and Cosmetic Act (FD&C Act)

- Section 721(a) – Color additives are deemed unsafe unless they are listed in the Code of Federal Regulations

- Section 721(b) – New color additives or new uses for color additives must undergo FDA's petition review process in order to be listed in the Code of Federal Regulations

Safety Standard for Color Additives

- Not defined in the FD&C Act
- Defined in the legislative history of the 1960 Amendments to the FD&C Act
- Safe for a color additive means “reasonable certainty of no harm” from the proposed use

How Does a Color Additive Get FDA Approval?

- Firm submits color additive petition to FDA
- Firm must provide information on:
  - Chemical description and uses
  - Exposure estimate
  - Toxicology studies
  - Environmental assessment
- Qualified FDA scientific experts review data
- If color additive is shown to be safe, it is listed with its specifications, uses, and restrictions

Information and Scientific Data Required in a Color Additive Petition

- Identity of the proposed color additive
- Physical, chemical, and biological properties
- Chemical specifications
- Manufacturing process description
- Stability data
- Intended uses and restrictions
- Labeling
- Tolerances and other limitations
- Analytical methods for enforcing chemical specifications
- Analytical methods for determining the color additive in products
- Safety studies
- Estimate of probable exposure
- Proposed regulation
- Proposed exemption from batch certification
- An environmental assessment or claim for categorical exclusion

Chemistry Review of a Color Additive Petition

- Guidance: “FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, or Cosmetics”
- Composition, impurities, analytical methods
- Need for batch certification

Should a New Color Additive Be Batch Certified?

- Petition must show why certification is not necessary for the protection of public health
- All certifiable and non-certifiable color additives must meet FDA's specifications

Estimate of Probable Exposure to a Color Additive

- Calculation of estimated daily intake (EDI) or dermal exposure
- For establishing uses, restrictions, specifications
- Exposure estimate used in safety review

Review of Safety Studies

- Guidance: “Redbook 2000—Toxicological Principles for the Safety Assessment of Food Ingredients”
- Evaluate toxicity studies
- For establishing safety, uses, restrictions, specifications

Environmental Assessment (21 CFR Part 25)

- Guidance: “Preparing a Claim of Categorical Exclusion or an Environmental Assessment”
- Finding of No Significant Impact (FONSI)
- Categorical exclusions
  - 21 CFR sections 25.30 and 25.32

Color Additive Listing Regulation

- Identity
- Specifications
- Uses and restrictions
- Labeling
- Exemption from certification *or*
- Requirement for certification

Color Additive Regulations

- Listed color additives
  - 21 CFR Part 73 (30 allowed in drugs)
    - Non-“FD&C” color additives
    - Exempt from certification
  - 21 CFR Part 74 (36 allowed in drugs)
    - “FD&C,” “D&C,” and “Ext. D&C” color additives
    - Required to be certified
  - 21 CFR Part 82
    - Most color additive lakes
    - Required to be certified

- Additional color additive requirements
  - 21 CFR Parts 70, 71, 80, and 81

Certified Color Additives

- "FD&C" color additives
- Synthetic organic dyes and pigments
  - "Synthetic" means man-made
  - "Organic" means made of carbon, hydrogen, nitrogen, oxygen, and sulfur
- Not much dye needed to achieve desired coloring
  - Dyes have high absorptivity values
- Required to be batch certified by FDA
  - Assures conformity to purity requirements
  - Strict limitations for lead, arsenic, and mercury (ppm levels)

FDA's Color Certification Program

- FDA's oldest user fee program
  - Result of 1938 FD&C Act
- Manufacturers submit samples from each new batch
  - OCAC's Color Certification Branch conducts analyses
  - Certificate and lot number issued if all specifications are met
  - 5-day turnaround
- Continual updating
  - Methodology
  - Instrumentation
- Web-based system
  - Certification database
  - Online certification requests
  - Electronic certification results

Common Names for Certified Color Additives

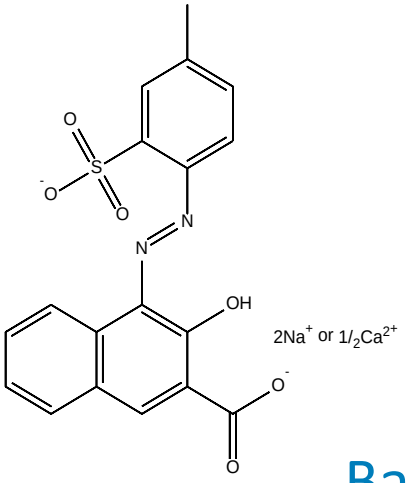
Common name:	*Certified as:*
• Allura Red AC ……	FD&C Red No. 40
• Brilliant Blue FCF …….	FD&C Blue No. 1
• Erythrosine ……..	FD&C Red No. 3
• Fast Green FCF ……..	FD&C Green No. 3
• Indigotine ……..	FD&C Blue No. 2
• Sunset Yellow FCF ……	FD&C Yellow No. 6
• Tartrazine ……..	FD&C Yellow No. 5

Certification Analyses

- Total color
  - Spectrophotometry
  - $TiCl_3$ titration
  - Gravimetric analysis
- Volatile matter
- Insoluble matter
- Extractable matter
- Salts (NaCl, Na_2SO_4)
- Intermediates

- Subsidiary colors
- Reaction by-products
- Aromatic amines
- Heavy metals
  - Lead, arsenic, mercury
  - Manganese, chromium

21 CFR 74.1307 - D&C Red No. 7



"Coal tar" dye (made synthetically)

Batch certified because likely to contain toxic impurities

Identity. The color additive D&C Red No. 7 is principally the calcium salt of 3-hydroxy-4-[(4-methyl-2-sulfophenyl)azo]-2-naphthalenecarboxylic acid (CAS Reg. No. 5281-04-9)

D&C Red No. 7 is an "azo" pigment

It is manufactured by diazotizing 2-amino-5-methylbenzenesulfonic acid and coupling with 3-hydroxy-2-naphthalenecarboxylic acid in the presence of calcium chloride

Chemical Specifications for D&C Red No. 7

- Sum of volatile matter (at 135 °C) and chlorides and sulfates (calculated as sodium salts), not more than 10%
- 1-[(4-Methylphenyl)azo]-2-naphthalenol, not more than 0.015%
- 2-Amino-5-methylbenzenesulfonic acid, calcium salt, not more than 0.2%
- 3-Hydroxy-2-naphthalenecarboxylic acid, calcium salt, not more than 0.4%
- 3-Hydroxy-4-[(4-methylphenyl)azo]-2-naphthalene-carboxylic acid, calcium salt, not more than 0.5%.
- p-Toluidine, not more than 15 ppm
- Lead, not more than 20 ppm
- Arsenic, not more than 3 ppm
- Mercury, not more than 1 ppm
- Total color, not less than 90%

Uses and Restrictions for D&C Red No. 7

- May be used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 milligrams per daily dose of the drug

Lakes

- Lakes – insoluble pigments formed from water-soluble straight colors, precipitants, and substrata

- Substrata – alumina, aluminum benzoate, barium sulfate, calcium carbonate, kaolin (clay), rosin, talc, titanium dioxide, and zinc oxide

- Precipitants – aluminum (3+), barium (2+), calcium (2+), potassium (1+), sodium (1+), strontium (2+), and zirconium (2+)

FD&C Lakes

- Straight color components permitted in drugs
  - FD&C Blue No. 1
  - FD&C Blue No. 2
  - FD&C Green No. 3
  - FD&C Red No. 40
  - FD&C Yellow No. 5
  - FD&C Yellow No. 6
- Must be made with alumina and aluminum (3+)
- Permitted in drugs for eye area use
  - FD&C Blue No. 1 aluminum lake
  - FD&C Red No. 40 aluminum lake
  - FD&C Yellow No. 5 aluminum lake
- Straight colors required to be certified prior to use in lakes

D&C Lakes

- Most D&C straight colors are not required to be certified in order to be used in lakes
  - e.g., D&C Red No. 28, D&C Yellow No. 10
- *Except:* Two D&C straight colors are required to be certified prior to use in lakes
  - D&C Red No. 33
  - D&C Red No. 36

Certification-Exempt Color Additives

- Non-“FD&C” color additives
- Must conform to purity requirements
  - Strict limitations for lead, arsenic, and mercury
- Manufacturers are responsible for compliance with CFR specifications

Certification-Exempt Color Additives

- Generally derived from plant, animal or mineral sources
  - One insect source
  - One cyanobacterium source
- Inorganic or organic compounds
  - May be synthesized or chemically processed
- Compared to certified color additives
  - Have less coloring power
    - Relatively large amounts may be needed to achieve desired coloring
  - Some are less stable and more variable in shade
  - Can vary in composition from batch to batch

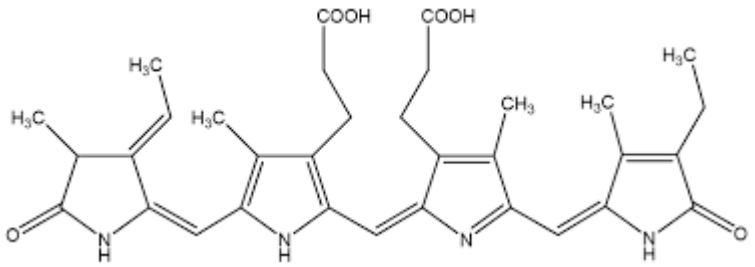
Color Additives Exempt from Certification Permitted in Drugs

- Plant sources
  - Annatto extract
  - Canthaxanthin
  - Potassium sodium copper chlorophyllin
- Animal source
  - Cochineal extract
  - Carmine
- Inorganic compounds
  - Alumina (aluminum oxide)
  - Chromium-cobalt-aluminum oxide
  - Synthetic iron oxide
  - Zinc oxide
  - Titanium dioxide
  - Mica-based pearlescent pigments
- Others
  - Caramel
  - Spirulina extract

21 CFR 73.1530- Spirulina extract New Color Additive for Use in Drugs

Identity.

Spirulina extract is prepared by the filtered aqueous extraction of the dried biomass of *Arthrospira platensis*. The coloring additive contains phycocyanins as the principal coloring components.



Chemical Specifications and Uses for Spirulina Extract

- Lead, not more than 2 ppm
- Arsenic, not more than 2 ppm
- Mercury, not more than 1 ppm
- Negative for microcystin toxins

- May be used for coloring coating formulations applied to drug tablets and capsules, at levels consistent with good manufacturing practice

Color Additive Labeling for Prescription Drugs

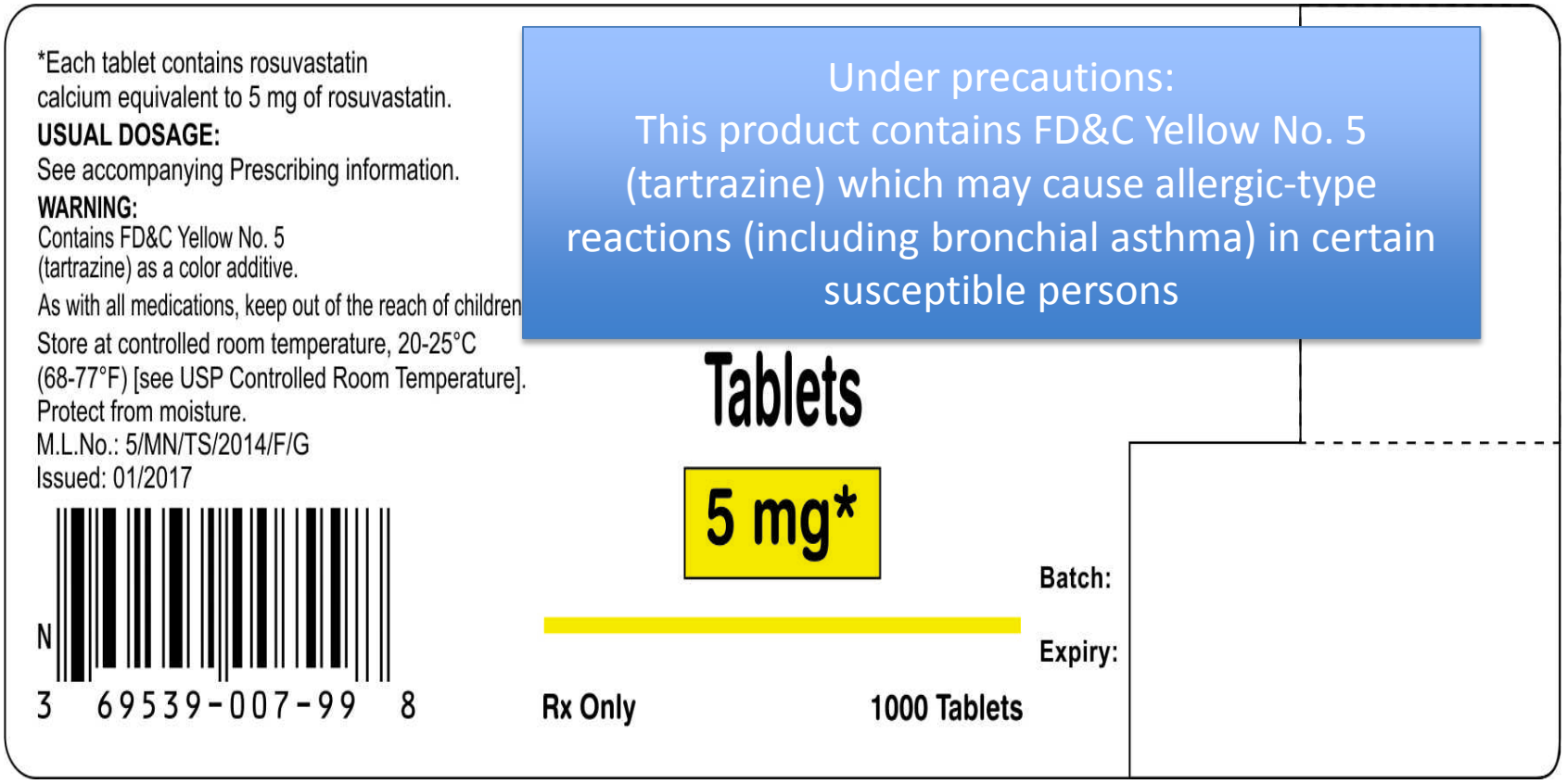
- Section 502(e) of the FD&C Act
  - Color additives in prescription drugs must be declared by their established (listed) names
    - e.g., D&C Yellow No. 10

- *Except* 21 CFR 201.100(b)(5)
  - Most color additives in non-oral prescription drugs can be called "coloring" unless required by another regulation
  - FD&C Yellow No. 5 and FD&C Yellow No. 6 must be declared by their listed names (21 CFR 201.20(c))

Additional Color Additive Labeling Requirement for FD&C Yellow No. 5

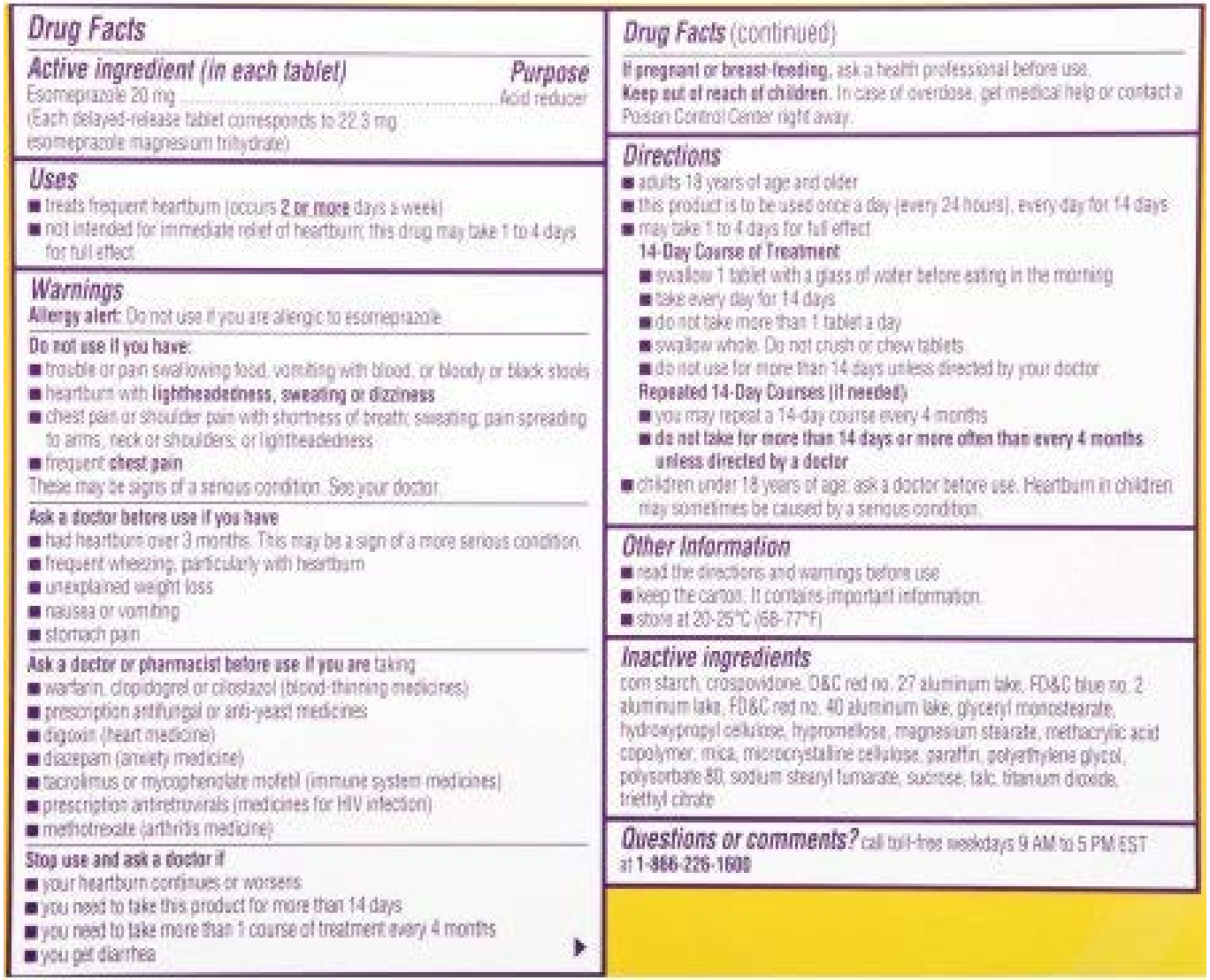
- 21 CFR 201.20(a)
- FD&C Yellow No. 5 must be labeled on all drugs
  - "Contains FD&C Yellow No. 5 (tartrazine) as a color additive" or "Contains color additives including FD&C Yellow No. 5 (tartrazine)"

- 21 CFR 74.1705 and 21 CFR 201.20(b)
- All prescription drug products containing FD&C Yellow No. 5 are also required to be labeled with a warning statement about possible allergic reactions
  - "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons."


*Each tablet contains rosuvastatin calcium equivalent to 5 mg of rosuvastatin.
USUAL DOSAGE:
See accompanying Prescribing information.
WARNING:
Contains FD&C Yellow No. 5 (tartrazine) as a color additive.
As with all medications, keep out of the reach of children
Store at controlled room temperature, 20-25°C (68-77°F) [see USP Controlled Room Temperature].
Protect from moisture.
M.L.No.: 5/MN/TS/2014/F/G
Issued: 01/2017
N
3 69539-007-99 8
Under precautions:
This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons
Tablets
5 mg*
Batch:
Expiry:
Rx Only
1000 Tablets

Color Additive Labeling for Over-The-Counter Drugs

- Section 502(e) of the FD&C Act
  - Color additives in over-the-counter drugs must be declared by their established (listed) names
- 21 CFR 201.66(c)(8) contains the inactive ingredient requirements
- 21 CFR 201.66(d) contains the Drug Facts labeling formats
  - Color additives must be declared in the “Inactive ingredients” section of the Drug Facts label



Drug Facts

Active ingredient (in each tablet) — **Purpose**

Esomeprazole 20 mg ..... Acid reducer

(Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)

Uses

- treats frequent heartburn (occurs **2 or more** days a week)
- not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect

Warnings

Allergy alert: Do not use if you are allergic to esomeprazole

Do not use if you have:

- trouble or pain swallowing food, vomiting with blood, or bloody or black stools
- heartburn with **lightheadedness, sweating or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**

These may be signs of a serious condition. See your doctor.

Ask a doctor before use if you have

- had heartburn over 3 months. This may be a sign of a more serious condition.
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are taking

- warfarin, clopidogrel or cilostazol (blood-thinning medicines)
- prescription antifungal or anti-yeast medicines
- digoxin (heart medicine)
- diazepam (anxiety medicine)
- tacrolimus or mycophenolate mofetil (immune system medicines)
- prescription antiretrovirals (medicines for HIV infection)
- methotrexate (arthritis medicine)

Stop use and ask a doctor if

- your heartburn continues or worsens
- you need to take this product for more than 14 days
- you need to take more than 1 course of treatment every 4 months
- you get diarrhea

Drug Facts (continued)

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults 18 years of age and older
- this product is to be used once a day (every 24 hours), every day for 14 days
- may take 1 to 4 days for full effect

14-Day Course of Treatment

- swallow 1 tablet with a glass of water before eating in the morning
- take every day for 14 days
- do not take more than 1 tablet a day
- swallow whole. Do not crush or chew tablets
- do not use for more than 14 days unless directed by your doctor

Repeated 14-Day Courses (if needed)

- you may repeat a 14-day course every 4 months
- **do not take for more than 14 days or more often than every 4 months unless directed by a doctor**
- children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.

Other Information

- read the directions and warnings before use
- keep the carton. It contains important information.
- store at 20-25°C (68-77°F)

Inactive ingredients

corn starch, crospovidone, D&C red no. 27 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, mica, microcrystalline cellulose, paraffin, polyethylene glycol, polysorbate 80, sodium stearyl fumarate, sucrose, talc, titanium dioxide, triethyl citrate

Questions or comments?

call toll-free weekdays 9 AM to 5 PM EST at **1-866-226-1609**

Drug Facts

Active ingredient (in each chewable tablet) — Purpose

Calcium carbonate 750 mg — Antacid

Uses for the relief of:

- acid indigestion
- heartburn
- sour stomach
- upset stomach associated with these symptoms

Warnings

Do not use if you have ever had an allergic reaction to this product or any of its ingredients

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

When using this product

- do not take more than 5 chewable tablets in a 24-hour period
- do not use the maximum dosage of this product for more than 2 weeks except under the advice and supervision of a physician
- constipation may occur

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

Drug Facts (continued)

Directions

- adults and children 12 years and over: fully chew then swallow 1 or 2 chewable tablets as symptoms occur, or as directed by a doctor
- children under 12 years: consult a doctor
- do not take more than 5 chewable tablets in a 24-hour period

Other information

- **each chewable tablet contains:** calcium 300 mg
- contains FD&C Yellow No. 5 (tartrazine) as a color additive
- store at room temperature. Avoid humidity.
- close cap tightly after use

Inactive ingredients acacia, carmine, carnauba wax, citric acid, corn starch, corn syrup, DL-alpha tocopherol, FD&C blue #1 aluminum lake, FD&C red #40 aluminum lake, FD&C yellow #5 lake (tartrazine), FD&C yellow #6, FD&C yellow #6 aluminum lake, FD&C yellow #6 lake, flavors, hydrogenated coconut oil, hydrogenated vegetable oil, lecithin, medium chain triglycerides, methyl paraben, modified starch, phosphoric acid, pregelatinized modified starch, propyl paraben, propylene glycol, shellac, sodium benzoate, sorbic acid, sorbitol, sugar, titanium dioxide, water, white wax

Questions or comments? 1-800-555-0100

Common Color Additive Violations

- Adulteration
  - Uncertified material used in a product
  - Non-permitted color additives used in a product
- Misbranding
  - Added color on ingredient label but not on finished product label

FDA's Enforcement of Drug Color Additive Requirements

- Authorized by FD&C Act and other applicable laws
  - 801(a)(3)
- Adulteration provisions - 501(a)(4)
- Misbranding provisions - 502(e and m)
- Import alerts
- Screening criteria for particular firms/products

Enforcement Tools for Color Additive Violations in Foods, Drugs, and Cosmetics

- Recalls
- Warning and untitled letters
- Detention, detention without physical examination (DWPE), import alerts
- Seizures
- Injunctions
- Prosecutions
- Civil money penalties

FDA's Enforcement of Drug Color Additive Requirements

- A drug may fail to comply with CGMP requirements for
  - Uncertified color additives
  - Non-permitted color additives
- Possible actions
  - Firm issued a warning letter *or*
  - Put on import alert
    - IA 66-40 Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs
    - IA 66-41 Detention Without Physical Examination of Unapproved New Drugs Promoted In The U.S.

Summary: Important Color Additive Requirements

- Only approved and listed color additives may be used in foods, drugs, cosmetics, and medical devices marketed in the U.S.
- All color additives must comply with the requirements in their listing regulations
  - Including purity requirements
- Color additives must be used appropriately
  - Manufacturers must consult the listing and labeling regulations
- Certified material must be used in products when required

Resources for Color Additives

- FDA's web site
  - **http://www.fda.gov**
- Summary of Color Additives for Use in United States in Foods, Drugs, Cosmetics, and Medical Devices
  - **http://www.fda.gov/ForIndustry/ColorAdditives/ColorAdditiveInventories/ucm115641.htm**
- Questions to druginfo@fda.hhs.gov

Thank you for your attention!