

MMQC-11-1195 \ PROTON PUMP INHIBITOR DRUGS / FDA MEDWATCH

FROM
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*****UNCLASSIFIED*****

SUBJ: MMQC-11-1195
PROTON PUMP INHIBITOR DRUGS / FDA MEDWATCH

01. EXCERPT FROM FDA MEDWATCH.

SAFETY ANNOUNCEMENT

THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) IS INFORMING THE PUBLIC THAT PRESCRIPTION PROTON PUMP INHIBITOR (PPI) DRUGS MAY CAUSE LOW SERUM MAGNESIUM LEVELS (HYPOMAGNESEMIA) IF TAKEN FOR PROLONGED PERIODS OF TIME (IN MOST CASES, LONGER THAN ONE YEAR). IN APPROXIMATELY ONE-QUARTER OF THE CASES REVIEWED, MAGNESIUM SUPPLEMENTATION ALONE DID NOT IMPROVE LOW SERUM MAGNESIUM LEVELS AND THE PPI HAD TO BE DISCONTINUED.

PPIS WORK BY REDUCING THE AMOUNT OF ACID IN THE STOMACH AND ARE USED TO TREAT CONDITIONS SUCH AS GASTROESOPHAGEAL REFLUX DISEASE (GERD), STOMACH AND SMALL INTESTINE ULCERS, AND INFLAMMATION OF THE ESOPHAGUS. IN 2009, APPROXIMATELY 21 MILLION PATIENTS FILLED PPI PRESCRIPTIONS AT OUTPATIENT RETAIL PHARMACIES IN THE UNITED STATES (SEE FOOTNOTE #2). PATIENTS WHO TAKE PRESCRIPTION PPIS USUALLY STAY ON THERAPY FOR AN AVERAGE OF ABOUT 180 DAYS (6 MONTHS) (SEE FOOTNOTE #3).

PRESCRIPTION PPIS INCLUDE NEXIUM (ESOMEPRAZOLE MAGNESIUM), DEXILANT (DEXLANSOPRAZOLE), PRILOSEC (OMEPRAZOLE), ZEGERID (OMEPRAZOLE AND SODIUM BICARBONATE), PREVACID (LANSOPRAZOLE), PROTONIX (PANTOPRAZOLE SODIUM), AND ACIPHEX (RABEPRAZOLE SODIUM). VIMOVO IS A PRESCRIPTION COMBINATION DRUG PRODUCT THAT CONTAINS A PPI (ESOMEPRAZOLE MAGNESIUM AND NAPROXEN). OVER-THE-COUNTER (OTC) PPIS INCLUDE PRILOSEC OTC (OMEPRAZOLE), ZEGERID OTC (OMEPRAZOLE AND SODIUM BICARBONATE), AND PREVACID 24HR (LANSOPRAZOLE).

IN CONTRAST TO PRESCRIPTION PPIS, OTC PPIS ARE MARKETED AT LOW DOSES AND ARE ONLY INTENDED FOR A 14 DAY COURSE OF TREATMENT UP TO 3 TIMES PER YEAR. FDA BELIEVES THAT THERE IS VERY LITTLE RISK OF HYPOMAGNESEMIA WHEN OTC PPIS ARE USED ACCORDING TO THE DIRECTIONS ON THE OTC LABEL.

LOW SERUM MAGNESIUM LEVELS CAN RESULT IN SERIOUS ADVERSE EVENTS INCLUDING MUSCLE SPASM (TETANY), IRREGULAR HEARTBEAT (ARRHYTHMIAS), AND CONVULSIONS (SEIZURES); HOWEVER, PATIENTS DO NOT ALWAYS HAVE THESE SYMPTOMS. TREATMENT OF HYPOMAGNESEMIA GENERALLY REQUIRES MAGNESIUM

SUPPLEMENTS. TREATMENT IN PATIENTS TAKING A PPI AND WHO HAVE HYPOMAGNESEMIA MAY ALSO REQUIRE STOPPING THE PPI.

HEALTHCARE PROFESSIONALS SHOULD CONSIDER OBTAINING SERUM MAGNESIUM LEVELS PRIOR TO INITIATION OF PRESCRIPTION PPI TREATMENT IN PATIENTS EXPECTED TO BE ON THESE DRUGS FOR LONG PERIODS OF TIME, AS WELL AS PATIENTS WHO TAKE PPIS WITH MEDICATIONS SUCH AS DIGOXIN, DIURETICS OR DRUGS THAT MAY CAUSE HYPOMAGNESEMIA. FOR PATIENTS TAKING DIGOXIN, A HEART MEDICINE, THIS IS ESPECIALLY IMPORTANT BECAUSE LOW MAGNESIUM CAN INCREASE THE LIKELIHOOD OF SERIOUS SIDE EFFECTS. HEALTHCARE PROFESSIONALS SHOULD CONSIDER OBTAINING MAGNESIUM LEVELS PERIODICALLY IN THESE PATIENTS.

INFORMATION ABOUT THE POTENTIAL RISK OF LOW SERUM MAGNESIUM LEVELS FROM PPIS WILL BE ADDED TO THE WARNINGS AND PRECAUTIONS SECTIONS OF THE LABELS FOR ALL THE PRESCRIPTION PPIS.

THIS COMMUNICATION IS IN KEEPING WITH FDA'S COMMITMENT TO INFORM THE PUBLIC ABOUT ITS ONGOING SAFETY REVIEW OF DRUGS. FDA IS CONTINUING TO REVIEW REPORTS OF POSSIBLE ADVERSE EVENTS AND DRUG INTERACTIONS WITH PPI DRUGS SUBMITTED TO OUR ADVERSE EVENT REPORTING SYSTEM.

[SEE DATA SUMMARY]

"ADDITIONAL INFORMATION FOR PATIENTS"

- SEEK IMMEDIATE CARE IF YOU (OR YOUR CHILD) EXPERIENCE AN ABNORMAL HEART RATE OR RHYTHM, OR SYMPTOMS SUCH AS A RACING HEARTBEAT, PALPITATIONS, MUSCLE SPASM, TREMOR OR CONVULSIONS WHILE TAKING A PPI DRUG. CHILDREN, ABNORMAL HEART RATES MAY CAUSE FATIGUE, UPSET STOMACH, DIZZINESS AND LIGHTHEADEDNESS.

- TELL YOUR HEALTHCARE PROFESSIONAL IF YOU HAVE EVER BEEN TOLD YOU HAVE LOW MAGNESIUM LEVELS IN YOUR BLOOD, OR IF YOU TAKE THE DRUG DIGOXIN, DIURETICS, OR OTHER DRUGS THAT MAY CAUSE HYPOMAGNESEMIA.

- HEALTHCARE PROFESSIONAL MAY OCCASIONALLY CHECK YOUR SERUM MAGNESIUM LEVEL (A BLOOD TEST) WHILE YOU ARE TAKING YOUR PRESCRIPTION PPI DRUG.

- DO NOT STOP TAKING YOUR PRESCRIPTION PPI DRUG WITHOUT TALKING TO YOUR HEALTHCARE PROFESSIONAL.

- DISCUSS ANY QUESTIONS OR CONCERNS ABOUT YOUR PPI DRUG WITH YOUR HEALTHCARE PROFESSIONAL.

- IF TAKE AN OVER-THE-COUNTER (OTC) PPI DRUG, FOLLOW THE DIRECTIONS ON THE PACKAGE CAREFULLY.

- MAKE SURE YOUR HEALTHCARE PROFESSIONAL KNOWS IF YOU HAVE BEEN TAKING AN OTC PPI DRUG FOR A LONG PERIOD OF TIME.

- REPORT ANY SIDE EFFECTS YOU EXPERIENCE TO THE FDA MEDWATCH PROGRAM USING THE INFORMATION IN THE CONTACT PARA BELOW.

"ADDITIONAL INFORMATION FOR HEALTHCARE PROFESSIONALS"

- CONSIDER OBTAINING SERUM MAGNESIUM LEVELS PRIOR TO INITIATION OF PRESCRIPTION PPI TREATMENT AND CHECKING LEVELS PERIODICALLY THEREAFTER FOR PATIENTS EXPECTED TO BE ON PROLONGED TREATMENT OR WHO TAKE PPIS WITH MEDICATIONS SUCH AS DIGOXIN OR DRUGS THAT MAY CAUSE HYPOMAGNESEMIA (E.G., DIURETICS).

- HYPOMAGNESEMIA OCCURS WITH BOTH LOOP DIURETICS (FUROSEMIDE, BUMETANIDE, TORSEMIDE, AND ETHACRYNICACID) AND THIAZIDE DIURETICS (CHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE, INDAPAMIDE, AND METOLAZONE). THESE AGENTS CAN CAUSE HYPOMAGNESEMIA WHEN USED AS A SINGLE AGENT OR WHEN COMBINED WITH OTHER ANTIHYPERTENSIVES (E.G., BETA-BLOCKERS, ANGIOTENSIN RECEPTOR BLOCKERS AND/OR ACE INHIBITORS).

- ADVISE PATIENTS TO SEEK IMMEDIATE CARE FROM A HEALTHCARE PROFESSIONAL IF THEY EXPERIENCE ARRHYTHMIAS, TETANY, TREMORS, OR SEIZURES WHILE TAKING PPIS. THESE MAY BE SIGNS OF HYPOMAGNESEMIA.

- CONSIDER PPIS AS A POSSIBLE CAUSE OF HYPOMAGNESEMIA, PARTICULARLY IN PATIENTS WHO ARE CLINICALLY SYMPTOMATIC.

- PATIENTS WHO DEVELOP HYPOMAGNESEMIA MAY REQUIRE PPI DISCONTINUATION IN ADDITION TO MAGNESIUMREPLACEMENT.

- BE AWARE THAT CONSUMERS EITHER ON THEIR OWN, OR BASED ON A HEALTHCARE PROFESSIONAL'S RECOMMENDATION, MAY TAKE OTC PPIS FOR PERIODS OF TIME THAT EXCEED THE DIRECTIONS ON THE OTC LABEL. THIS IS CONSIDERED AN OFF-LABEL (UNAPPROVED) USE. HEALTHCARE PROFESSIONALS SHOULD COMMUNICATE THE RISK OF HYPOMAGNESEMIA PATIENTS IF THEY ARE RECOMMENDING PROLONGED USE OF AN OTC PPIS.

- REPORT ADVERSE EVENTS INVOLVING PPIS TO THE FDA MEDWATCH PROGRAM, USING THE INFORMATION IN THE CONTACT US.

"DATA SUMMARY"

FDA HAS REVIEWED REPORTS FROM THE ADVERSE EVENT REPORTING SYSTEM (AERS), MEDICAL LITERATURE, AND PERIODIC SAFETY UPDATE REPORTS FOR CASES OF HYPOMAGNESEMIA IN PATIENTS UNDERGOING PROLONGED TREATMENT WITH PPI MEDICATIONS. FDA'S REVIEW FOCUSED ON 38 CASES IN AERS AND 23 CASES REPORTED IN THE LITERATURE (WHICH INCLUDE AT LEAST 8 CASES OF THE IDENTIFIED AERS CASES) (SEE FOOTNOTE # 4,5,6,7,8,9,10,11). THE AERS CASE SERIES EXCLUDED PATIENTS WHO WERE ON DIURETICS. THE CASES FROM THE LITERATURE INCLUDED PATIENTS ON DIURETICS WHEN EITHER (A) CHANGE IN DIURETIC WAS NOT ASSOCIATED WITH AN IMPROVEMENT IN SERUM MAGNESIUM LEVEL, OR (B) WHEN INCREASE IN SERUM MAGNESIUM LEVEL OCCURRED WITH DOCUMENTED PPI DISCONTINUATION. THE FDA REVIEW SUGGESTS

AN ASSOCIATION BETWEEN HYPOMAGNESEMIA-RELATED SERIOUS ADVERSE EVENTS AND PROLONGED PPI USE. HOWEVER, BECAUSE HYPOMAGNESEMIA IS LIKELY UNDER-RECOGNIZED AND UNDER-REPORTED, THE AVAILABLE DATA ARE INSUFFICIENT TO QUANTIFY AN INCIDENCE RATE FOR HYPOMAGNESEMIA WITH PPI THERAPY.

HYPOMAGNESEMIA HAS BEEN REPORTED IN ADULT PATIENTS TAKING PPIs FOR AT LEAST THREE MONTHS, BUT MOST CASES OCCURRED AFTER A YEAR OF TREATMENT. APPROXIMATELY ONE-QUARTER OF THESE CASES REQUIRED DISCONTINUATION OF PPI TREATMENT IN ADDITION TO MAGNESIUM SUPPLEMENTATION. SOME CASES CITED BOTH POSITIVE DECHALLENGE AS WELL AS POSITIVE RECHALLENGE (I.E., RESOLUTION OF HYPOMAGNESEMIA WITH PPI CESSATION AND RECURRENT HYPOMAGNESEMIA WITH PPI RESUMPTION). AFTER DISCONTINUING THE PPI, THE MEDIAN TIME REQUIRED FOR THE MAGNESIUM TO NORMALIZE WAS ONE WEEK. AFTER RESTARTING THE PPI, THE MEDIAN TIME TO DEVELOP HYPOMAGNESEMIA AGAIN WAS TWO WEEKS. IN MOST CASES REVIEWED THE PATIENTS DID NOT CONTINUE ON PPIs AFTER THE HYPOMAGNESEMIA WAS TREATED.

EXAMPLES OF POSITIVE DECHALLENGE IN TWO PATIENTS INCLUDE A 63-YEAR-OLD WOMAN AND A 67-YEAR-OLD MAN WHO WERE BOTH TREATED WITH PPIs FOR 6 AND 11 YEARS, RESPECTIVELY. BOTH PATIENTS PRESENTED WITH SEIZURES AND HYPOMAGNESEMIA. ALTHOUGH BOTH PATIENTS' HYPOMAGNESEMIA PARTIALLY RESOLVED WITH INTRAVENOUS REPLACEMENT, IN BOTH CASES DISCONTINUATION OF PPI TREATMENT WAS NECESSARY TO STOP ONGOING SYMPTOMS AND TO STOP MAGNESIUM LOSS.

CLINICALLY SERIOUS ADVERSE EVENTS WERE CONSISTENT WITH COMMONLY REPORTED SIGNS AND SYMPTOMS OF HYPOMAGNESEMIA, WHICH ARE SIMILAR TO THE SIGNS AND SYMPTOMS REPORTED WITH HYPOCALCEMIA. THE SERIOUS EVENTS INCLUDED TETANY, SEIZURES, TREMORS, CARPO-PEDAL SPASM, ATRIAL FIBRILLATION, SUPRAVENTRICULAR TACHYCARDIA, AND ABNORMAL QT INTERVAL. HYPOMAGNESEMIA ALSO PRODUCES IMPAIRED PARATHYROID HORMONE SECRETION WHICH MAY LEAD TO HYPOCALCEMIA. IN CASES WHERE COMPREHENSIVE CLINICAL LABORATORY DATA WERE AVAILABLE, MOST PATIENTS HAD CONCOMITANT HYPOCALCEMIA AND NORMAL PARATHYROID HORMONE LEVELS. THEREFORE, THESE FINDINGS CONFIRM HYPOMAGNESEMIA AS THE PRIMARY DEFICIT.

THE MECHANISM RESPONSIBLE FOR HYPOMAGNESEMIA ASSOCIATED WITH LONG TERM PPI USE IS UNKNOWN; HOWEVER, LONG TERM USE OF PPIs MAY BE ASSOCIATED WITH CHANGES IN INTESTINAL ABSORPTION OF MAGNESIUM (SEE FOOTNOTE #5).

OTC PPIs ARE MARKETED FOR THE TREATMENT OF FREQUENT HEARTBURN UNDER THE BRAND NAMES PRILOSEC OTC, ZEGERID OTC, AND PREVACID 24 HR. OTC PPIs ARE LABELED FOR 14 DAYS OF USE, AND THIS TREATMENT COURSE MAY BE REPEATED EVERY 4 MONTHS, UP TO 3 TIMES PER YEAR. FDA ACKNOWLEDGES THAT CONSUMERS, EITHER ON THEIR OWN, OR BASED ON A HEALTHCARE PROFESSIONAL'S RECOMMENDATION, MAY TAKE THESE PRODUCTS FOR PERIODS OF TIME THAT EXCEED THE DIRECTIONS ON THE OTC LABEL. THIS IS CONSIDERED AN OFF-LABEL (UNAPPROVED) USE, BASED ON THE DIRECTIONS OF USE FOR OTC PPIs. HEALTHCARE PROFESSIONALS SHOULD BE AWARE OF THE RISK OF HYPOMAGNESEMIA IF THEY ARE RECOMMENDING USE OF OTC PPIs FOR LONGER PERIODS OF TIME

THAN IN THE OTC PPI LABEL. FDA BELIEVES THAT OTC PPIS CARRY VERY LITTLE RISK OF HYPOMAGNESEMIA WHEN USED ACCORDING TO THE PACKAGE DIRECTIONS, AND THEREFORE THE DRUG FACTS BOX FOR THE OTC PPIS WILL NOT BE CHANGED TO INCLUDE THE RISK OF HYPOMAGNESEMIA.

1. SDI, VECTOR ONE(r): NATIONAL (VONA). 2002- 2010.DATA EXTRACTED 3-12-10.

2. SDI, VECTOR ONE(r): TOTAL PATIENT TRACKER (TPT). 2002-2009. DATA EXTRACTED 3-24-10.

3. IMS HEALTH, IMS HEALTH PLAN CLAIMS DATABASETM

4. BROEREN MA, GEERDINK EA, VADER HL, VAN DEN WALL BAKE AW. HYPOMAGNESIUM INDUCED BY SEVERAL PROTON PUMP INHIBITORS. ANN INTERN MED (NOV 17, 2009). 151(10); 755-756.

5. CUNDY T, DISSANAYAKE A. SEVERE HYPOMAGNESEMIA IN LONG-TERM USERS OF PROTON-PUMP INHIBITORS. CLINICA ENDOCRINOLOGY (2008). 69; 338-341.

6. EPSTEIN M, MCGRATH S, LAW F. PROTON-PUMP INHIBITORS AND HYPOMAGNESEMIA HYPOPARATHYROIDISM. NEJM. OCTOBER 26, 2006. 355;17:1,834-1,836.

7. HOORN EJ, MD, VAN DER HOEK J, DE MAN RA, KUIPERS EJ, ET AL. A CASE SERIES OF PROTON PUMP INHIBITORINDUCED HYPOMAGNESEMIA. AM J KIDNEY DIS. FEBRUARY 25 2010. (EPUB).

8. KUIPERS MT, THANG HD, ARNTZENIUS AB. HYPOMAGNESAEMIA DUE TO USE OF PROTON PUMP INHIBITORS A REVIEW. NETH J MED (MAY 2009). 67(5);169-172.

9. METZ DC, SOSTEK MB, RUSZNIEWSKI P, FORSMARK CE, ET AL. EFFECTS OF ESOMEPRAZOLE ON ACID OUTPUT IN PATIENTS WITH ZOLLINGER-ELLISON SYNDROME OR IDIOPATHIC GASTRIC ACID HYPERSECRETION. AM J GASTROENTEROL.(DECEMBER 2007). 102(12); 2648-2654.

10. SHABAJEE N, LAMB E, STURGESS I, SUMATHIPALA R. OMEPRAZOLE AND REFRACTORY HYPOMAGNESEMIA. BMJ (2008): 337; 173-175.

11. MACKAY JD AND BLADON PT. HYPOMAGNESAEMIA DUE TO PROTON-PUMP

INHIBITOR

THERAPY: A CLINICAL CASE SERIES. QJ MED 2010; 103:387-395.

CONTACT

HEALTHCARE PROFESSIONALS AND PATIENTS ARE ENCOURAGED TO REPORT ADVERSE EVENTS OR SIDE EFFECTS RELATED TO THE USE OF THESE PRODUCTS TO THE FDA'S MEDWATCH SAFETY INFORMATION AND ADVERSE EVENT REPORTING PROGRAM:

- COMPLETE AND SUBMIT THE REPORT ONLINE: WWW.FDA.GOV/MEDWATCH/REPORT.HTM<[HTTP://WWW.FDA.GOV/MEDWATCH/REPORT.HTM](http://www.fda.gov/medwatch/report.htm)>

- DOWNLOAD FORM

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OR CALL 1-800-332-1088 TO REQUEST A REPORTING FORM, THEN COMPLETE AND RTN TO THE ADDRESS ON THE PRE-ADDRESSED FORM, OR SUBMIT BY FAX TO 1-800-FDA-0178.

02. PASS MSG TO MEDICAL LOG OFCRS, CMD CHANNELS, PHARMACY, GASTROENTEROLOGY, CLINICAL STAFF, RISK MANAGEMENT, HEALTHCARE PROFESSIONALS, FAMILY PRACTICE, MED STAFF, SUPPLY OFCRS, AND SUPPORTED ACTYS/CTRS.

03. AUTHORITY: DODD 5105.22 AND DODD 6025.13. ADDITIONALLY:

A. ARMY: SEE ARMY REGULATION (AR) 40-61, 28 JANUARY 2005, CHAPTER 4, AND THE DEPARTMENT OF THE ARMY SUPPLY BULLETIN (SB 8-75-11) FOR APPLICABLE POLICIES AND PROCEDURES.

B. AIR FORCE: AF ACTIVITIES WILL TAKE ACTION AS PRESCRIBED IN AFI 41-209, MEDICAL LOGISTICS SUPPORT, CHAPTERS 3 AND 9. FOR MAJCOMS & NGB--THIS MSG HAS BEEN TRANSMITTED TO ALL DESIGNATED SUBORDINATE MEDICAL ACTIVITIES.

04. SERVICE SPECIFIC POCS ARE AS FOLS (FAX NOS. ARE AVAILABLE 24 HRS);

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