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SEÑOR
SUPERINTENDENTE DE INDUSTRIA Y CC
E. S. D.

SM

REF: **Expediente 13-156-481**

TÍTULO SOLICITADO: **TABLETA ORALMENTE DESINTEGRADORA**

PUBLICACIÓN: **Gaceta 672 de 31/07/2013, N° de publicación 1054.**

PRIORIDAD: **JP 2010/270276 de 03/12/2010**

SOLICITANTE: **TAKEDA PHARMACEUTICAL COMPANY LIMITED.**

APODERADO: **LUZ CLEMENCIA SUAREZ DE PAEZ.**

TRÁMITE: **SUSTENTACION DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**,dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 28 de octubre de 2013, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primera instancia, se objetaron reivindicaciones como la 8 y 10, en tanto las mismas hacen mención explícita de "dosificaciones", lo que supone la pretensión de amparar métodos de tratamiento, excluidos de patentabilidad, de acuerdo con la Decisión 486 de 2000.

- De otro lado, fueron objetadas las reivindicaciones 18, 19, 20 y 21, referidas específicamente a pesos finales por tableta, proporción en peso, forma física del comprimido final, tiempo de desintegración y durezas, u otras especificaciones del producto terminado, en tanto dichos parámetros no tienen por sí mismos naturaleza inventiva, pues corresponden a una simple caracterización de resultados, rutinaria en cualquier práctica de preformulación en laboratorio.

- Se acreditó, de otro lado, que la combinación farmacológica entre un inhibidor de bomba de protones y ácido acetil salicílico, opcionalmente con un antiácido, es una estrategia de formulación ampliamente conocida en el estado de la técnica, rutinaria y carente por completo de nivel inventivo.

- También se demostró que la solicitud no es nueva, según lo descrito en la publicación internacional **WO 97/25064 "*Oral pharmaceutical dosage forms comprising a proton pump inhibitor an a NSAID*"**, en tanto el documento encontrado se relaciona con una forma de dosificación oral multicapas, que comprende un inhibidor de la bomba de protones protegido por una capa entérica, con uno o más AINES, por lo cual concluimos que la solicitud no es nueva dado que contiene **todas las características técnicas** esenciales de la reivindicación 1 de la solicitud colombiana en trámite.

- Mediante el arte previo encontrado, quedó suficientemente claro que la pauta de tratamiento bajo la cual se combinan inhibidores de la bomba de protones tales como el omeprazol, lansoprazol y pantoprazol, con AINES como el ácido acetil salicílico, era bien conocida y usada clínicamente a la fecha de presentación de la solicitud, por ende el problema técnico ya había sido solucionado con antelación, el cual además consideró la opción de contener un antiácido o algún agente alcalino, tal como se pretende proteger, incluso con los mismos excipientes, desintegrantes y lubricantes entre los que se encuentra la carboximetilcelulosa. Se comprueba entonces mediante la

oposición presentada oportunamente que en ninguna de sus modalidades la presente solicitud en trámite es nueva.

- A pesar de lo anterior, se empleó un segundo documento, la publicación japonesa **JP 2002-29964 de 29/01/2002 "*Solid pharmaceutical composition*"**que revela composiciones farmacéuticas en forma de tableta multicapa que comprende partículas de antiácido, tales como hidróxido de magnesio y de aluminio, coprecipitados de hidróxido de magnesio y carbonato ácido de sodio, carbonato de magnesio, carbonato de calcio, coprecipitados de hidróxido de aluminio y carbonato ácido de sodio, en una capa y en la otra capa un componente activo que puede ser ácido acetilsalicílico, lo cual le aporta nulidad inventiva a la solicitud colombiana habida cuenta que el primer documento mencionado revela la combinación explícita con inhibidores de la bomba de protones. Dicho documento revela de forma puntual los excipientes, el aceite hidrogenado, y la carboximetilcelulosa utilizada para formulaciones que contienen los AINES que conforman la formulación reivindicada por la solicitud colombiana y que conllevan la obtención de las propiedades deseables que logran solucionar el problema técnico propuesto.

- Así las cosas, evidenciamos que la combinación de los dos documentos encontrados anulan totalmente el nivel inventivo de la solicitud e incluso la novedad ya que la formulación que se pretende proteger y sus posibles combinaciones se describían ampliamente en el estado de la técnica.

  De aquí que, según lo previamente enseñado, podemos evidenciar que la reivindicación independiente (1) y sus dependientes no cumplen con los requisitos de patentabilidad, ya que las composiciones sugeridas allí no son nuevas ni inventivas, más aún, cuando ya se sabía cómo resolver el mismo problema técnico propuesto por la solicitud colombiana CO 13-156-481, con la misma ventaja técnica.

II. COMPLEMENTO DE INFORMACIÓN.

Por si no fueses suficientes los argumentos dados en la oposición presentada oportunamente, queremos someter a su consideración, adicionalmente, los siguientes:

- Enfatizamos en el hecho que al encontrarse todas las características técnicas esenciales en un solo documento tal como lo es el **WO 97/25064** la solicitud colombiana no cumple con el requisito de patentabilidad de **novedad**.

- Adicional a lo anterior, hemos encontrado un tercer documento: la publicación internacional **WO 2005/076987** del 25 de agosto de 2005, titulada **"Combination of proton pump inhibitor, buffering agent, and nonsteroidal anti-inflammatory agent"** que sugiere la fabricación de composiciones que comprenden un inhibidor de la bomba de protones, uno o varios agentes buffer y un antiinflamatorio no esteroide para tratar desordenes relacionados con ácido gástrico y desórdenes inflamatorios:

(57) **Abstract:** Pharmaceutical compositions comprising a proton pump inhibitor, one or more buffering agent and a nonsteroidal anti-inflammatory drug are described. Methods are described for treating gastric acid related disorders and treating inflammatory disorders, using pharmaceutical compositions comprising a proton pump inhibitor, a buffering agent, and a nonsteroidal anti-inflammatory drug.

Esta anterioridad es un ejemplo más de que la solución al problema técnico propuesto por **la solicitud colombiana en trámite estaba resuelto previamente** en el estado de la técnica, ya que el tipo de combinación que se pretende proteger tenía ampliamente establecida su finalidad en el arte.

Así mismo, la anterioriad incluye los mismos inhibidores de la bomba de protones que pretende proteger la solicitud en trámite en su reivindicación 9, es decir, omeprazol, lansoprazol, pantoprazol, rabeprazol (ver pág 5) en conjunto con derivados de ácido salicílico como la aspirina (ver pág 6).

Proton pump inhibitors include, but are not limited to, omeprazole, hydroxyomeprazole, esomeprazole, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, periprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof. In one embodiment, the proton pump inhibitor is omeprazole or a free base,

(...)

pyrazoles such as difenamizole and epirozole; pyrazolones such as apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, prostaglandins, ramifenazone, suxibuzone, and thiazolinobutazone; salicylic acid derivatives such as acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole

(...)

Se revela además, el excipiente carboximetilcelulosa por medio del cual se recubre el ácido acetil salicílico (pag 8), veamos:

> hydroxypropyl methyl ethers, methylcellulose polymers, ethylcelluloses and mixtures thereof, polyvinyl alcohol, hydroxyethylcelluloses, carboxymethylcelluloses, salts of carboxymethylcelluloses, polyvinyl alcohol, polyethylene glycol co-polymers, monoglycerides, triglycerides, polyethylene glycols, modified food starch, acrylic polymers,
>
> (...)

Adicionalmente, las composiciones que revela el documento en mención enseñan que el inhibidor de la bomba de protones debe ir recubierto tal y como lo propone la solicitud colombiana (ver pág 9):

> Compositions are provided that include (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, wherein at least some of the proton pump inhibitor is coated, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor
>
> (...)

Por último, la composición del arte previo contiene todos los antiácidos que pretende proteger la solicitud en trámite, seleccionados entre óxidos de metal, hidróxidos de metal, carbonato de metal alcalino- térreo y glicinato de aluminio tal y como aparecen en las reivindicaciones 3, 4, 5, 6, 7 (ver pág 11 y 12):

> Compositions including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, wherein the buffering agent is an alkaline earth metal salt or a Group IA metal selected from a bicarbonate salt of a Group IA metal, a carbonate salt of a Group IA metal. The buffering agent can be, but is not limited to, an amino acid, an alkali metal salt of an amino acid, aluminum hydroxide, aluminum hydroxide/magnesium
>
> (...)
>
> carbonate/calcium carbonate co-precipitate, aluminum magnesium hydroxide, aluminum hydroxide/magnesium hydroxide co-precipitate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, calcium acetate, calcium bicarbonate, calcium borate, calcium carbonate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium phthalate, calcium phosphate, calcium succinate, calcium tartrate, dibasic sodium phosphate, dipotassium hydrogen phosphate, dipotassium phosphate, disodium hydrogen phosphate, disodium succinate, dry aluminum hydroxide gel, L-arginine, magnesium acetate, magnesium aluminate, magnesium borate, magnesium bicarbonate,
>
> (...)

sodium acetate, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate, sodium gluconate, sodium hydrogen phosphate, sodium hydroxide, sodium lactate, sodium phthalate, sodium phosphate, sodium polyphosphate, sodium pyrophosphate, sodium sesquicarbonate, sodium succinate, sodium tartrate, sodium tripolyphosphate, synthetic hydrotalcite, tetrapotassium pyrophosphate, tetrasodium pyrophosphate, tripotassium phosphate, trisodium phosphate, trometamol, and mixtures thereof. In particular, the buffering agent can be sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide, magnesium carbonate, aluminum hydroxide, and mixtures thereof.

(...)

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS

- Publicación internacional WO 97/25064 del 17 de julio de 1997, pág abstract, 2, 3, 6, 13, 15, 16, 19.
- Publicación japonesa JP 2002-29964 del 29 de enero de 2002, pág abstract, 1, 3, 4, 5, 7, 8, 9, 10, 11.
- Publicación internacional WO 2005/076987 del 25 de agosto de 2005 y titulada "Combination of proton pump inhibitor, buffering agent, and nonsteroidal anti-inflammatory agent" pág abstract, 4, 5, 6, 8, 9, 11, 12.

Señor Superintendente,

JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

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(71) Applicant (*for all designated States except US*): **SANTARUS, INC.** [US/US]; 10590 West Ocean Air Drive, Suite 200, San Diego, CA 92130 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **PROEHL, Gerald, T.** [US/US]; 10590 West Ocean Air Drive, Suite 200, San Diego, CA 92130 (US). **OLMSTEAD, Kay** [US/US]; 7423 Park Village Road, San Diego, CA 92129 (US). **HALL, Warren** [US/US]; 12929 Via Esperia, San Diego, CA 92130 (US).

(74) Agents: **GUISE, Jeffrey, W.** et al.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94306-1050 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/076987 A2

(54) Title: COMBINATION OF PROTON PUMP INHIBITOR, BUFFERING AGENT, AND NONSTEROIDAL ANTI-INFLAMMATORY AGENT

(57) Abstract: Pharmaceutical compositions comprising a proton pump inhibitor, one or more buffering agent and a nonsteroidal anti-inflammatory drug are described. Methods are described for treating gastric acid related disorders and treating inflammatory disorders, using pharmaceutical compositions comprising a proton pump inhibitor, a buffering agent, and a nonsteroidal anti-inflammatory drug.

Attempts have been undertaken to modify the structure of NSAIDs in order to prevent undesired side-effects. The new family of NSAIDs which selectively inhibit only cyclooxygenase-II ("COX-II inhibitors") represent one such advance. Although COX-II inhibitors are believed to cause less stomach irritation than the older non-selective NSAIDs, they still have the potential to cause irritation, ulceration, bleeding and perforation of the lining of the stomach.

Furthermore, there is emerging evidence of a protective association between aspirin/NSAIDs and various cancer types such as esophageal cancer, lung cancer, colorectal cancer, breast cancer, and prostate cancer. *See, e.g.,* Randall E. Harris *et al., Inverse Association of Breast Cancer and NSAIDs: Results from the Women's Health Initiative* (WH), AACR, Volume 44 (March 2003); Gonzalez-Perez A; *Effects of Non-Steroidal Anti-Inflammatory Drugs on Cancer Sites Other than the Colon and Rectum: a Meta-Analysis*, BMC Cancer 3(1):28 (2003); DA Corley *et al., Protective Association of Aspirin/NSAIDs and Esophageal Cancer: A Systematic Review and Meta-Analysis*; Gastroenterology 2003 124:47-56; Khuder *et al., Breast Cancer and NSAID Use: A Meta Analysis*, British Journal of Cancer (2001) 84, 1188-1192. It is believed that COX-II may be important in certain types of cancer pathogenesis and animal studies suggest that long-term use of NSAIDs may prevent the development of these tumors.

One promising solution to the problem of healing and preventing NSAID associated upper gastrointestinal problems, like ulcers and dyspeptic symptoms in patients needing continuous NSAID treatment, is to combine the NSAID treatment with an anti-ulcer drug approved for the healing and/or prophylaxis of NSAID associated gastrointestinal side-effects such as prostaglandin analogues, H_2-receptor antagonists, and proton pump inhibitors ("PPIs"). Additionally, since many of the patients suffering from inflammatory disorders also suffer from gastric acid related disorders, there is a need for pharmaceutical formulations useful for co-administering a proton pump inhibitor for the treatment of a gastric acid related disorder and a nonsteroidal anti-inflammatory drug useful for treatment of an inflammatory disorder.

SUMMARY OF THE INVENTION

Pharmaceutical compositions including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount

sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, are provided herein. Methods are provided for treating gastric acid related disorders and treating inflammatory disorders in a subject, using pharmaceutical compositions of the present invention. Methods are also provided for preventing gastric acid related disorders during long-term administration of NSAID in a subject for the purpose of reducing the risk of heart attack or certain types of cancers by administering the subject pharmaceutical compositions of the present invention.

Proton pump inhibitors include, but are not limited to, omeprazole, hydroxyomeprazole, esomeprazole, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, periprazole, ransoprazole, pariprazole, leminoprazole; or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof. In one embodiment, the proton pump inhibitor is omeprazole or a free base, free acid, salt, hydrate, ester, amide, enantiomer, isomer, tautomer, polymorph, or prodrug thereof. Compositions can contain between about 5 mgs to about 200 mgs of proton pump inhibitor, specifically about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, or about 80 mg of the proton pump inhibitor. In alternative embodiments, compositions can contain between about 250-3000 mg of proton pump inhibitor.

Nonsteroidal anti-inflammatory drugs include, but are not limited to aminoarylcarboxylic acid derivatives such as enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate, and tolfenamic acid; arylacetic acid derivatives such as aceclofenac, acemetacin, alclofenac, amfenac, amtolmetin guacil, bromfenac, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin, isofezolac isoxepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, and zomepirac; arylbutyric acid derivatives such as bumadizon, butibufen, fenbufen, xenbucin; arylcarboxylic acids such as clidanac, ketorolac, tinoridine; arylpropionic acid derivatives such as alminoprofen, benoxaprofin, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprozin, piketoprofin, pirprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximoprofen, and zaltoprofen;

pyrazoles such as difenamizole and epirozole; pyrazolones such as apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, prostaglandins, ramifenazone, suxibuzone, and thiazolinobutazone; salicylic acid derivatives such as acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphtyl salicylate, olsalazine, parsalmide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalate, sulfasalazine; thiazinecarboxamides such as ampiroxicam, droxicam, isoxicam, lomoxicam, piroxicam, and tenoxicam, cyclooxygenase-II inhibitors ("COX-II") such as Celecoxib, Vioxx, Relafen, Lodine, and Voltaren; and others such as epsilon-acetamidocaproic acid, s-adenosylmethionine, 3-amino-4-hydroxybutytic acid, amixetrine, bendazac, benzydamine, α-bisabolol, bucololome, difenpiramide, ditazol, emorfazone, fepradinol, guaiazulene, nabumetone, nimesulide, oxaceprol, paranyline, perisoxal, proquazone, tenidap and zilenton.

Compositions are provided such that an initial serum concentration of the proton pump inhibitor is greater than about 0.1 μg/ml at any time within about 30 minutes after administering the formulation. Initial serum concentration of the proton pump inhibitor can be greater than about 0.1 μg/ml at any time within about 15 minutes. Initial serum concentration of the proton pump inhibitor can be greater than about 0.2 μg/ml at any time within about 1 hour after administration, greater than about 0.3 μg/ml at any time within about 45 minutes after administration.

Compositions are provided such that a serum concentration of greater than about 0.1 μg/ml can be maintained from at least about 30 minutes to about 1 hour after administration of the composition. Compositions are provided such that a serum concentration of proton pump inhibitor greater than about 0.1 μg/ml can be maintained from at least about 15 minutes to about 30 minutes. Compositions are provided such that a serum concentration of greater than about 0.1 μg/ml can be maintained from at least about 30 minutes to about 45 minutes. Compositions are provided such that a serum concentration of greater than about 0.25 μg/ml can be maintained from at least about 30 minutes to about 1 hour. Compositions are provided such that a serum concentration of greater than about 0.25 μg/ml can be maintained from at least about 30 minutes to about 45 minutes. Compositions are provided such that a serum

provided wherein at least about 50% of total area under the serum concentration time curve (AUC) for the proton pump inhibitor occurs within about 1.5 hours after administration of a single dose of the composition to the subject. Compositions are provided wherein at least about 50% of total area under the serum concentration time curve (AUC) for the proton pump inhibitor occurs within about 1 hour after administration of a single dose of the composition to the subject.

Compositions are provided wherein, upon oral administration to the subject, the composition provides a pharmacokinetic profile such that the proton pump inhibitor reaches a maximum serum concentration within about 1 hour after administration of a single dose of the composition. Compositions are provided wherein the maximum serum concentration is reached within about 45 minutes after administration of the composition. Compositions are provided wherein the maximum serum concentration is reached within about 30 minutes after administration of the composition.

Compositions are provided wherein at least some of the proton pump inhibitor is microencapsulated with a material that enhances the shelf-life of the pharmaceutical composition. Compositons are provided wherein at least some of the nonsteroidal anti-inflammatory drug is microencapsulated with a material that enhances the shelf-life of the pharmaceutical composition. Compositions are provided wherein some of the proton pump inhibitor and some of the nonsteroidal anti-inflammatory drug are microencapsulated with a material that enhances the shelf-life of the pharmaceutical composition. Materials that enhance the shelf-life of the pharmaceutical composition include, but are not limited to, cellulose hydroxypropyl ethers, low-substituted hydroxypropyl ethers, cellulose hydroxypropyl methyl ethers, methylcellulose polymers, ethylcelluloses and mixtures thereof, polyvinyl alcohol, hydroxyethylcelluloses, carboxymethylcelluloses, salts of carboxymethylcelluloses, polyvinyl alcohol, polyethylene glycol co-polymers, monoglycerides, triglycerides, polyethylene glycols, modified food starch, acrylic polymers, mixtures of acrylic polymers with cellulose ethers, cellulose acetate phthalate, sepifilms, cyclodextrins; and mixtures thereof. The cellulose hydroxypropyl ether can be, but is not limited to, Klucel® or Nisso HPC.. The cellulose hydroxypropyl methyl ether can be, but is not limited to, Seppifilm-LC, Pharmacoat®, Metolose SR, Opadry YS, PrimaFlo, BenecelMP824, or BenecelMP843. The mixture of methylcellulose and hydroxypropyl and methylcellulose polymers can be, but is not limited to, Methocel®, Benecel-MC, or

Metolose®. The ethylcellulose or mixture thereof can be, but are not limited to, Ethocel®, BenecelMO43, Celacal, Cumibak NC, and E461. The polyvinyl alcohol can be, but is not limited to, Opadry AMB. The acrylic polymers or mixtures thereof include, but are not limited to, Eudragits® EPO, Eudragits® RD100, and Eudragits® E100. Other materials that enhance the shelf-life of the pharmaceutical composition include, but are not limited to, Natrosol®, Aqualon®-CMC, and Kollicoat IR®. The material that enhances the shelf-life of the pharmaceutical composition can further include other compatible materials such as an antioxidant, a plasticizer, a buffering agent, and mixtures thereof.

Compositions are provided that include (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, wherein at least some of the proton pump inhibitor is coated, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, wherein the nonsteroidal anti-inflammatory drug is useful for treating an inflammatory disorder. Inflammatory diseases include, but are not limited to, reperfusion injury to an ischemic organ (*e.g.*, reperfusion injury to the ischernic myocardium), myocardinal infarction, inflammatory bowel disease, rheumatoid arthritis, osteroarthritis, psoriasis, organ transplant rejection, inflammation of the ear, eye, throat, nose or skin, organ preservation, a female or male sexual dysfunction, radiation-induced injury, asthma, respiratory disorder, metastasis, influenza, incontinence, stroke, burn, trauma, acute pancreatistis, pyelonephristis, hepatitis, an autoilnmune disease, and immunological disorder, senile dementia, insulin-dependent diabetes mellitus, disseminated intravascular coagulation, fatty embolism, Alzheimer's disease, adult or infantile respiratory disease, carcinogenesis in a neonate, hemorrhage in a neonate, restenosis, atherogenesis, angina, (particularly chronic, stable angina pectoris), ischemic disease, congestive heart failure or pulmonary edema associated with acute myocardial infarction, thrombosis, hypertension (especially hypertension associated with cardiovascular surgical procedures), platelet aggregation, platelet adhesion, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, cerebrovascular ischemic events, and the like.

Compositions are provided that include (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor wherein at least some of the proton pump

to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, wherein the proton pump inhibitor is useful for treating a gastric acid related disorder and the nonsteroidal anti-inflammatory drug is useful for treating an inflammatory disorder or other disease treatable by a nonsteroidal anti-inflammatory drug.

Compositions are provided that include (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, wherein the nonsteroidal anti-inflammatory drug is useful for decreasing the risk of heart attack.

Compositions are provided that include (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, wherein the pharmaceutical composition is useful for preventing cancer.

Compositions are provided that include (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, wherein the nonsteroidal anti-inflammatory drug is a COX-II inhibitor.

Compositions including (a) a therapeutically effective amount of at least one acid labile proton pump inhibitor, (b) at least one buffering agent in an amount sufficient to increase gastric fluid pH to a pH that prevents acid degradation of at least some of the proton pump inhibitor in the gastric fluid, and (c) a therapeutically effective amount of at least one nonsteroidal anti-inflammatory drug, wherein the buffering agent is an alkaline earth metal salt or a Group IA metal selected from a bicarbonate salt of a Group IA metal, a carbonate salt of a Group IA metal. The buffering agent can be, but is not limited to, an amino acid, an alkali metal salt of an amino acid, aluminum hydroxide, aluminum hydroxide/magnesium

carbonate/calcium carbonate co-precipitate, aluminum magnesium hydroxide, aluminum hydroxide/magnesium hydroxide co-precipitate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum glycinate, calcium acetate, calcium bicarbonate, calcium borate, calcium carbonate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium phthalate, calcium phosphate, calcium succinate, calcium tartrate, dibasic sodium phosphate, dipotassium hydrogen phosphate, dipotassium phosphate, disodium hydrogen phosphate, disodium succinate, dry aluminum hydroxide gel, L-arginine, magnesium acetate, magnesium aluminate, magnesium borate, magnesium bicarbonate, magnesium carbonate, magnesium citrate, magnesium gluconate, magnesium hydroxide, magnesium lactate, magnesium metasilicate aluminate, magnesium oxide, magnesium phthalate, magnesium phosphate, magnesium silicate, magnesium succinate, magnesium tartrate, potassium acetate, potassium carbonate, potassium bicarbonate, potassium borate, potassium citrate, potassium metaphosphate, potassium phthalate, potassium phosphate, potassium polyphosphate, potassium pyrophosphate, potassium succinate, potassium tartrate, sodium acetate, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate, sodium gluconate, sodium hydrogen phosphate, sodium hydroxide, sodium lactate, sodium phthalate, sodium phosphate, sodium polyphosphate, sodium pyrophosphate, sodium sesquicarbonate, sodium succinate, sodium tartrate, sodium tripolyphosphate, synthetic hydrotalcite, tetrapotassium pyrophosphate, tetrasodium pyrophosphate, tripotassium phosphate, trisodium phosphate, trometamol, and mixtures thereof. In particular, the buffering agent can be sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium oxide, magnesium hydroxide, magnesium carbonate, aluminum hydroxide, and mixtures thereof.

Compositions are provided as described herein, where the buffering agent to proton pump inhibitor ratio is at least 10:1; at least 12:1; at least 15:1; at least 20:1; at least 22:1; at least 25:1; at least 30:1; at least 35:1; and at least 40:1.

Compositions are provided as described herein, where the buffering agent is sodium bicarbonate and is present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg proton pump inhibitor. Compositions are provided as described herein, where the buffering agent is a mixture of sodium bicarbonate and magnesium hydroxide, and each buffering agent is present in about 0.1 mEq/mg proton pump inhibitor to about 5 mEq/mg proton pump inhibitor. Compositions are provided as described herein, where the buffering agent is a