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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E S D

REF Expediente 03-095-518

**TÍTULO SOLICITADO "COMPOSICION PARENTERAL RECONSTITUIBLE
QUE CONTIENE UN INHIBIDOR COX-2"**

**PUBLICACIÓN Gaceta 553 de 30-06-2005, numero de publicacion
189**

PRIORIDAD US 60/281,058 de 03-04-2001

SOLICITANTE Pharmacia Corporation

APODERADO Emilio Ferrero

TRÁMITE SUSTENTACIÓN DE OPOSICIÓN

J SÉ LUIS REYES VILLAMIZAR, identificado como aparece al pie de mi firma, reconocido apoderado de los opositores en el trámite de la referencia, estando dentro de los términos de la prórroga solicitada, por medio del presente escrito me permito ratificar y sustentar los argumentos del escrito principal de oposición, también radicado dentro del plazo de ley ante esa entidad

I RATIFICACIÓN

Reitero a su Despacho la solicitud de negar el beneficio patentano para la totalidad de las reivindicaciones contenidas en el expediente en referencia, por los argumentos que fueron definidos en el escrito de oposición del 27 de septiembre de 2005, en donde se hace explícito que la formulación parenteral reconstituible que contiene un Inhibidor de COX-2, junto con un agente amortiguador y otros agentes parenteralmente aceptables para formar una solución inyectable revelados en la solicitud colombiana CO-03-095-518, carece de nivel inventivo

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debido a la materia revelada en la patente CN1235018A publicada antes de la fecha de pñondad de la solicitud en trámite, pues en ese documento se reivindica una inyección liofilizada para reconstitución, cuya preparación incluye también un agente amortiguador y otros excipientes parenteralmente aceptables Aunque es claro que el principio activo incluído en esta formulación es Pantoprazol sódico, no lo es menos que el documento en cuestión describe en esencia la misma materia ahora reivindicada – la formulacion farmacéutica en general-, circunstancia que demuestra la carencia de Nivel Inventivo de dicha solicitud

II COMPLEMENTO DE INFORMACIÓN

Como adición a lo expuesto en el punto precedente y en el escrito inicial de oposición, ruego al Despacho se sirva tener en cuenta de igual manera la materia revelada en el siguiente documento

A La patente de los Estados Unidos de América US 5,932,598 "PRODRUGS OF BENZENESULFONAMIDE CONTAINING COX-2 INHIBITORS" publicada el 3 de agosto de 1999, en la cual se revela en la columna 80, más específicamente en el ejemplo 82 una composición que comprende

- N-[[4-(5-metyl-2-phenylisoxazol-4-yl) phenyl]sulfonyl] propanamide "PARECOXIB", sal sódica 40 mg
- Buffer Fosfato, pH 7.5 (10mM) 2ml
- Manitol 40mg,

El manitol es adicionado a la solución de buffer de fosfato, luego la sal sódica de Parecoxib se adiciona y la solución resultante es liofilizada

Resulta interesante establecer una comparación detallada entre dicha patente y las reivindicaciones de la solicitud colombiana en trámite, así

US 5,932, 598 (3-08-1999)	Solicitud Colombiana 03-095-518
Ejemplo 82 Composición que comprende • N-[[4-(5-methyl-2-phenylisoxazol-4-yl) phenyl] sulfonyl] propanamide sal sódica (Parecoxib) INHIBIDOR DE	Rv 1 Composición que comprende a) un inhibidor de COX-2, prodrogas y/o sales de esta b) un agente amortiguador c) otros ingredientes excipientes,

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US 5,932, 598 (3-08-1999)	Solicitud Colombiana 03-095-518
COX-2 • Buffer Fosfato pH 7.5 AMORTIGUADOR • Manitol 40mg EXCIPIENTES • Solucion Liofilizada	que es reconstituible en un líquido solvente parenteralmente aceptable para formar una solución inyectable Rv 2 y 3 El agente terapéutico comprende una sal soluble en agua prodroga o sal de una prodroga de un inhibidor de COX-2 como Valdecoxib Rv 4 El agente terapéutico comprende Parecoxib o una sal de ella Rv 5 El agente terapéutico comprende Parecoxib sódico Rv 9 La composición que consiste esencialmente del agente terapéutico y el agente amortiguador Rv 10, 11, 12 El agente amortiguador es fosfato dibásico de sodio Rv 13 La composición luego de la reconstitución tiene un pH entre 7 y 9 Rv 22 Se menciona una etapa de liofilización

Es fácil concluir aquí que la patente US 5,932,598 no solo revela el empleo del mismo inhibidor de COX-2 o prodroga o sal del mismo (pues "Parecoxib" es la prodroga o profármaco de "Valdecoxib") sino que también menciona el uso de un Buffer o Amortiguador (Buffer de Fosfato) y otros excipientes farmacéuticamente aceptables. Supone lo expuesto que la composición revelada anticipa el objeto de la solicitud en trámite de manera general desde 1999, circunstancia que demuestra que la solicitud en cuestión carece de nivel inventivo, y aun de novedad.

B Otro documento que se considera relevante en este caso es el relacionado con la monografía de Parecoxib sódico Xaptek™, disponible para el público en la dirección electrónica http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_28_CC-FDA-Tab-Q.pdf, en donde se describe lo siguiente: *"Parecoxib sodium was developed as a parenteral analgesic for the management of acute pain. It is chemically designated as the sodium salt of N-[4-(5-methyl-3-phenylisoxazol-4-yl) phenyl]sulfonyl propanamide. Parecoxib sodium is rapidly (T_{1/2}=15-30 min) and essentially completely converted via enzymatic hydrolysis to the pharmacologically active moiety valdecoxib [4-(5-methyl-3-*

phenylisoxazol-4-yl)benzenesulfonamide] and propionic acid This enzymatic conversion occurs primarily in the liver The terminal half-life ($T_{1/2}$) of valdecoxib is approximately 8 hours Following intravenous (IV) administration of parecoxib, peak (T_{max}) plasma levels of valdecoxib are achieved in approximately 30 minutes, for intramuscular (IM) injection, peak plasma levels are achieved in approximately 1 hour

Parecoxib sodium is supplied as a sterile, preservative-free, lyophilized powder equivalent to 20 mg or 40 mg parecoxib in single-use vials Inactive ingredients include dibasic sodium phosphate heptahydrate, and phosphonic acid and/or sodium hydroxide (which might be added to adjust the pH to 8.0) Parecoxib sodium is designed to be reconstituted with 1 mL (20 mg vials) or 2 mL (40 mg vials) sterile saline for injection (0.9% sodium chloride) Subrayado y negrita fuera del texto

De la simple lectura de los párrafos anteriores, accesibles al público desde el año 2000, se aprecia que la materia revelada en la solicitud en curso de novedad y nivel inventivo pues la citada monografía de Parecoxib sódico describe un inhibidor de la COX-2 "Parecoxib sódico" en forma de polvo liofilizado junto con un agente amortiguador como buffer de fosfatos (amortiguador), el cual es reconstituido con solución salina normal para inyección para formar así la solución inyectable

C Como demostración adicional de la carencia de Nivel Inventivo de la solicitud en curso, y sin perjuicio de admitir que el documento PCT/WO99/21585 publicado en mayo 6 de 1999 se refiere a una combinación de principios activos, hago notar que en él se revelan composiciones farmacéuticas que comprenden al menos un inhibidor de COX-2 y puede ser administrada por vía oral, parenteral, rectal, ocular, transdérmica nasal y auncular

Los ejemplos 1E y 3E señalan preparaciones inyectables que contienen

UP 454-21*	0.1%	LT 454-21*	0.1%
Acetaminofen	1%	Codeina	0.1%
PEG 400	30%	PEG 400	30%
Ethyl Alcohol	20%	Ethyl alcohol	10%
Agua para Inyección q s p	100%	Agua para Inyección q s p	100%

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* Donde UP 454-21 o LT 454-21 son inhibidores de la COX-2 según el solicitante

Por lo todo lo expuesto, reitero mi solicitud para que sea negada la solicitud en cuestión y como consecuencia de ello, se ordene el archivo del expediente debido al evidente incumplimiento de lo dispuesto en los artículos 14, 16 y 18 de la Decisión 486 de 2000

III PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, en particular de las allegadas por el suscrito a los expedientes mencionados en este escrito, la siguiente

- 1 Patente americana US 5,932,598 publicada el 3 de agosto de 1999, columna 80 ejemplo 82
- 2 Páginas 1 a 4 de la monografía de Parecoxib Sódico, Xaptek™
- 3 Aplicación Internacional WO 99/21585 publicada 6 de mayo de 1999, páginas 10,12 y 14

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C C 79'152 473 de Usaquén
T P A 44 655 de C S J



US005932598A

United States Patent [19]

[11] Patent Number 5,932,598

Talley et al.

[45] Date of Patent Aug. 3, 1999

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[54] PRODRUGS OF BENZENESULFONAMIDE-CONTAINING COX-2 INHIBITORS

[75] Inventors: John J Talley Brentwood, Mo., James W Malecha, Libertyville, Ill., Stephen Bertenshaw, Brentwood, Mo., Matthew J Granato, St. Louis, Mo., Jeffrey Carter, Chesterfield, Mo., Jinglin Li, Chesterfield, Mo., Srinivasa Nagarajan, Chesterfield, Mo., David L. Brown, Chesterfield, Mo., Donald J Engler, Jr., Chesterfield, Mo., Thomas D Fanning, Elmhurst, Ill., Ish K Khanna, Vernon Hills, Ill., Xiangdong Xu, Evanston, Ill., Richard M Weller, Lake Bluff, Ill.

[73] Assignee: G. D. Searle & Co., Skokie, Ill.

[21] Appl. No. 09/005,610

[22] Filed: Jan. 12, 1998

Related U.S. Application Data

[63] Continuation of application No. 08/031,514, Apr. 12, 1996 abandoned.

[51] Int. Cl.⁶ A61K 31/42 A61K 31/415
A61K 31/16; C07D 211/72, C07D 211/84,
C07D 263/32, C07D 403/02, C07D 223/04,
C07D 231/10; C07D 207/00; C07D 207/12

[52] U.S. Cl. 514/341, 514/374, 514/397
514/399 514/403; 514/406; 514/602; 546/274 1
546/290; 548/225; 548/228, 548/229; 548/314 7
548/315 1 548/235, 548/328.5 548/335.5,
548/375 1 548/376 1 548/377 1 548/359.5,
548/541, 548/544 548/556, 564/61, 564/84

[58] Field of Search --- 546/274 1 290;
548/225, 228, 229, 314 7, 315 1 315.4,
235 375 1 376 1, 377 1 359.5 541 544,
556, 335 5, 328.5, 514/341, 374, 397, 399,
403, 406, 602, 564/84 61

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Primary Examiner—Floyd D. Higel
Attorney, Agent, or Firm—Joseph W. Balock

[57] ABSTRACT

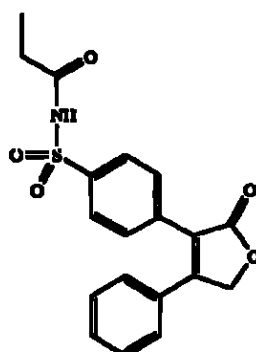
Prodrugs of COX-2 inhibitors are described as being useful in treating inflammation and inflammation-related disorders.

72 Claims, No Drawings

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EXAMPLE 81



N-[[4-(3-Phenyl-2,3-dihydro-2-oxofuran-4-yl)
phenyl]sulfonyl]propanamide

Step 1

Preparation of 3,4-diphenyl-2-(5H)-furanone

A solution of phenacyl bromide (16.540 g, 83.1 mmol) and phenylacetic acid (11.612 g, 83.3 mmol) in acetonitrile was treated with triethylamine (9.23 g, 91.4 mmol) and the solution was stirred at room temperature for 1 hour. The solution was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (30 mL, 0.234 mol) and the solution was stirred at room temperature for 1 hour. The solution was diluted with 3N HCl and extracted with ethyl acetate. The combined extract was washed with 3N HCl, brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford a solid. The solid was crystallized from hexanes/ethyl acetate 1:1 to afford the furanone (11.627 g, 59%); mp 103.8–104.9° C. ^1H NMR ($CDCl_3$ /300 MHz) 7.45–7.25 (m, 10H), 5.18 (s, 2H). FAB/MS m/z 237 (M+H). Anal. Calc'd for $C_{16}H_{12}O_2$, 0.83% H_2O C 80.66; H 5.17. Found: C, 80.67; H, 5.29.

Step 2

Preparation of 3-[(4-aminosulfonyl)phenyl]-4-phenyl-2-(5H)-furanone

To 20 mL of stirring chlorosulfonic acid cooled to -5° C was added 3,4-diphenyl-2-(5H)-furanone (Step 1) (3.160 g, 13.4 mmol) portionwise over 30 minutes. The solution was warmed to room temperature and maintained at that temperature for 16 hours. The reaction mixture was diluted with dichloromethane and quenched into ice water. The phases were separated and the aqueous phase extracted with dichloromethane, the combined dichloromethane extract was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was diluted with dichloromethane and added to excess concentrated NH_4OH . The mixture was stirred for 1 hour. The phases were separated and the aqueous phase was extracted with dichloromethane. The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a white solid that was crystallized from aqueous ethanol to afford pure 3-[(4-aminosulfonyl)phenyl]-4-phenyl-2-(5H)-furanone (2.110 g, 50%); mp 225.5–226.5° C. ^1H NMR ($CDCl_3$ /300 MHz) 7.79 (d, 2H, J=8.4 Hz), 7.41 (d, 2H, J=8.4 Hz), 6.38 (br, 2H), 5.09 (s, 2H). FAB/MS m/z 316 (m+H). Anal. Calc'd for $C_{16}H_{12}NO_2S$ C, 60.94; H, 4.16; N, 4.44. Found: C, 60.86; H, 4.18; N, 4.40.

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Step 3

Preparation of N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide

A solution of 3-[(4-aminosulfonyl)phenyl]-4-phenyl-2-(5H)-furanone (Step 2) (209 mg, 0.663 mmol), triethylamine (134 mg, 1.33 mmol), N,N -dimethylaminopyridine (58 mg, 0.475 mmol) in THF was treated with propionic anhydride (129 mg, 0.994 mmol) at room temperature for 45 minutes. The solution was diluted with 3N HCl and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give an oil that was crystallized from ethyl acetate/hexanes to afford the acylated sulfonamide as a white solid (179 mg, 73%); mp 176.2–178.1° C. ^1H NMR ($CDCl_3$ /300 MHz) 8.56 (s, 1H), 8.06 (d, 2H, J=8.7 Hz), 7.62 (d, 2H, J=8.7 Hz), 7.44–7.22 (m, 5H), 5.23 (s, 2H), 2.30 (q, 2H, J=7.5 Hz), 1.08 (t, 3H, J=7.5 Hz). FAB/MS m/z 372 (M+H). Anal. Calc'd for $C_{19}H_{17}NO_2S$ C, 61.44; H, 4.61; N, 3.77. Found: C, 61.44; H, 4.61; N, 3.77.

EXAMPLE 82

A composition is prepared having the following components:

N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide sodium salt 40 mg
phosphate buffer pH 7.5 (10 mM) 2 ml
mannitol 40 mg
Mannitol (40 mg) is added to phosphate buffer solution (2 ml). The N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide sodium salt is added and the resulting solution is lyophilized.

Biological Evaluation

Rat Carrageenan Foot Pad Edema Test

The carrageenan foot edema test was performed with materials, reagents and procedures essentially as described by Winter et al., (*Proc. Soc. Exp. Biol. Med.*, 111:544 (1962)). Male Sprague-Dawley rats were selected in each group so that the average body weight was as close as possible. Rats were fasted with free access to water for over sixteen hours prior to the test. The rats were dosed orally (1 mL) with compounds suspended in vehicle containing 0.5% methylcellulose and 0.025% surfactant or with vehicle alone. One hour later a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline was administered and the volume of the injected foot was measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot was again measured. The average foot swelling in a group of drug-treated animals was compared with that of a group of placebo-treated animals and the percentage inhibition of edema was determined (Osterman and Bhven, *Laboratory Models for Testing NSAIDs in Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The % inhibition shows the % decrease from control paw volume determined in this procedure and the data for selected compounds in this invention are summarized in Table I.

Rat Carrageenan-Induced Analgesia Test

The rat carrageenan analgesia test was performed with materials, reagents and procedures essentially as described by Hargreaves et al. (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats were treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan the rats were placed in a special plexiglass container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under

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Parecoxib Sodium

NDA 21-294

Medical Officer Review

Submission Date	September 11, 2000
Received Date	September 12, 2000
Review Date	December 1, 2000
Drug Name	Xaptek™
Generic Name	parecoxib sodium
Chemical Name	sodium salt of N-([4-(5-methyl-3-phenylisoxazol 4-yl)phenyl]sulfonyl)propanamide
Applicant	G D Searle & Co
Related Reviews	Statistics, Cardio-Renal, Gastrointestinal, Biopharm, Chemistry, Pharmacology, Medical (valdecoxib)
Pharmacologic category	COX-2 inhibitor (parenteral)
Proposed Indication	Management of pain (postoperative and preemptive)
	Opioid Sparing
Dosage forms and route	For injection, 20 and 40 mg
Submission type	Original NDA
Materials Reviewed	Primary documents- N93-00-07-815 N93-00-07-816 N93-00-07-804 I93-00-06-035

Ong NDA # 21-294
HFD-550/Div File
HFD-550/PM/Schmidt
HFD-550/Pharm/Yang
HFD-550/Chem/Bhavnagri
HFD-550/Biopharm/Bashaw
HFD-550/Statistics/Lin
HFD-550/MO/Witter/Goldkind

(James Witter, M D , Ph D Medical Officer)

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Parecoxib Executive Summary

Significant Issues

- Parecoxib is a new molecular entity and represents the first parenteral "COX-2 selective" agent to seek approval in the U S
- Although the single dose data in several surgical situations have established that parecoxib sodium at 40 mg is efficacious compared to placebo, this is not the case for single doses of 20 mg.
- Multiple dose data with parecoxib sodium are limited and do not allow for characterization of the safe and effective dose, or dosing interval after the first dose
- The proposed labeling claims for management of postoperative pain or for the preemptive treatment of pain or for opioid sparing with parecoxib sodium are not supported by the data available in this NDA either due to insufficient data or lack of replication of results
- Safety data from the CABG trial suggest that certain subgroups of patients may be at increased risks for serious adverse events. Furthermore, these data can not exclude the possibility of an important safety liability associated with parecoxib sodium, particularly with repeated doses, over placebo

Highlights

- Parecoxib sodium is a parenteral prodrug of the orally available compound valdecoxib which is under concurrent review. This dual development has impacted, and confounded, the ability to make clear distinctions in terms of the safety and efficacy associated with parecoxib sodium
- Most (approximately two thirds) of the data on safety and efficacy in the original NDA were obtained from patients or subjects exposed to single doses of parecoxib sodium. While such data is fundamental to supporting the efficacy and safety of parecoxib sodium, it is insufficient to fully characterize the safety and efficacy of this compound
- It is unclear, from the currently available data, whether the efficacy associated with parecoxib sodium in a surgical setting is sufficient to balance the observed adverse events. However, owing to the nature of the surgical setting or use of medications both during and after the surgery, interpretation of adverse events is not always

straightforward. There are no data regarding the use of parecoxib sodium in an emergency or trauma-like setting

BACKGROUND AND OVERVIEW

In acutely painful conditions, parenteral administration of analgesic medication can provide a rapid and sustained onset of analgesia, especially in patients unable to ingest or tolerate oral medication. Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are

commonly used parenteral analgesics for the management of acute pain. However, their use can be limited by a wide spectrum of adverse effects. These adverse effects can actually slow the postoperative rehabilitation process and compound the risk inherent in any surgical procedure. These adverse outcomes may be particularly true for elderly patients, patients with a history of peptic ulcer disease, patients in whom respiratory depression should be avoided, patients with an increased susceptibility to perioperative bleeding, and patients with compromised renal function.

Parenteral opioids are the mainstay of acute postoperative pain management in the inpatient setting. However, a number of frequent adverse effects associated with their use have been identified. These include respiratory depression, nausea, vomiting, sedation, urinary retention, constipation, decreased gastrointestinal (GI) motility, and paralytic ileus. These adverse effects often impede postoperative rehabilitation and limit their use in the ambulatory surgical setting. Failure to provide adequate management of pain, either due to inadequate analgesic efficacy or sub-optimal treatment due to concerns about potential adverse effects, can contribute substantially to reduced quality of life among patients experiencing acute pain. Due to the growing number of outpatient surgical procedures, additional symptoms such as somnolence and dizziness that frequently accompany the use of opioids may further limit these agents as a treatment for postoperative analgesia, particularly in an outpatient setting.

The current standard of care for analgesia in the perioperative setting consists of opioids, with adjunctive use of NSAIDs ("multimodal analgesia"). In less severe cases, NSAIDs alone are sufficient to provide effective postoperative analgesia. The selection of multimodal drug therapy (including opioids and NSAIDs) for the management of acute pain is based on a number of principles, including the analgesic efficacy of centrally acting opioids, the peripheral anti-inflammatory and analgesic effects of NSAIDs, and the synergy that can be observed between these two modes of treatment. Although both opioids and NSAIDs are effective analgesics, neither are without safety and tolerability concerns that may become exaggerated in an already compromised postsurgical patient population.

Toradol® (ketorolac tromethamine) is currently the only approved parenteral NSAID for use in the United States. It is effective and may be used as an adjunct to opioids for the management of postoperative pain. However, the use of ketorolac is associated with a number of adverse effects characteristic of NSAIDs, including upper GI ulceration and bleeding (particularly in the elderly), reduction in renal function, hemostatic impairment

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(decrease in platelet aggregation and increase in duration of bleeding), and bronchospasm. Owing to concerns about safety, the use of ketorolac has been limited to five days and cannot be administered preoperatively.

Parecoxib sodium (SC-69124A, $C_{19}H_{17}N_2O_4SNa$) is a water-soluble inactive prodrug of valdecoxib (SC-65872), a highly selective inhibitor of cyclooxygenase-2 (COX-2). Parecoxib sodium was developed as a parenteral analgesic for the management of acute pain. It is chemically designated as the sodium salt of N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide. Parecoxib sodium is rapidly ($T_{1/2}=15-30$ min) and essentially completely converted via enzymatic hydrolysis to the pharmacologically active moiety valdecoxib [4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide] and propionic acid. This enzymatic conversion occurs primarily in the liver. The terminal half-life ($T_{1/2}$) of valdecoxib is approximately 8 hours. Following intravenous (IV) administration of parecoxib, peak (T_{max}) plasma levels of valdecoxib are achieved in approximately 30 minutes; for intramuscular (IM) injection, peak plasma levels are achieved in approximately 1 hour.

Parecoxib sodium is supplied as a sterile, preservative-free, lyophilized powder equivalent to 20 mg or 40 mg parecoxib in single-use vials. Inactive ingredients include dibasic sodium phosphate heptahydrate, and phosphoric acid and/or sodium hydroxide (which might be added to adjust the pH to 8.0). Parecoxib sodium is designed to be reconstituted with 1 mL (20 mg vials) or 2 mL (40 mg vials) sterile saline for injection (0.9% sodium chloride).

Based on the *in vitro* inhibition of recombinant human COX-1 ($IC_{50}=140$ μ m) and COX-2 ($IC_{50}=0.005$ μ m), valdecoxib (the active moiety of parecoxib sodium) exhibits approximately 28,000-fold selectivity for COX-2 versus COX-1. On the basis of the COX-2 specificity of valdecoxib, it was hypothesized that parecoxib would provide a superior therapeutic index compared to currently approved conventional ketorolac and mild opioids and yield significant benefits for patients who require relief of acute pain.

According to the Sponsor, as a novel COX-2 specific parenteral agent, parecoxib has been developed to have an improved safety profile (particularly with respect to the absence of respiratory depression, lack of sedative effects, absence of effects on platelet function, and absence of UGI ulceration). The demonstration that a compound has analgesic efficacy for moderate to severe pain along with improved safety relative to currently available alternatives would represent a valuable addition to the therapeutic armamentarium for acute pain management. Parecoxib was designed to meet an unmet medical need of an efficacious anti-inflammatory parenteral analgesic that would reduce or eliminate the deleterious side effects that accompany opioid analgesics or conventional NSAIDs such as ketorolac tromethamine.

The goal of the nonclinical pharmacology program emphasized models in which pain and inflammation were mediated primarily by prostaglandin production via COX-2. The efficacy of parecoxib in animal models of inflammation and pain was consistent with its conversion to valdecoxib *in vivo*. In dose-response comparisons, parecoxib and

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ A61K 45/06	A1	(11) International Publication Number WO 99/21585 (43) International Publication Date 6 May 1999 (06.05.99)
(21) International Application Number PCT/IB98/01789 (22) International Filing Date 19 October 1998 (19 10.98) (30) Priority Data. 97/13426 27 October 1997 (27 10.97) FR (71) Applicant: LABORATOIRES UP1A (FR/FR) 12R, rue Danton, Boite postale 325, F-92506 Rueil-Malmaison Cedex (FR). (72) Inventors: CAMBORDE, François, 19, avenue du 18 Juin 1940, F-92500 Rueil-Malmaison (FR). CLOAREC Aïx, 26, rue des Bismes, F-78510 Triel-sur-Seine (FR). NICOLAI, Eric, 2, rue Marie-Levasseur, F-92500 Rueil-Malmaison (FR). TEULON, Jean-Marie, 13, avenue Gilbert, F-78170 La Celle-Saint-Cloud (FR). (74) Agent: MAYS Julie; Bristol-Myers Limited Company Patent Dept. Swakeleys House, Milton Road Ickenham Uxbridge UB10 8NS (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (OH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments</i>	
(54) Title: PHARMACEUTICAL COMBINATION OF A CYCLOOXYGENASE-2 INHIBITOR AND ACETAMINOPHEN OR AN OPIATE (57) Abstract The object of the present invention is a pharmaceutical composition, characterized in that it comprises as active principle, a combination of a cyclooxygenase-2 inhibitor and a compound selected from acetaminophen and the opiates.		

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738**Example 1E** Injectable preparation

5	UP 454-21 ..	0.1%
	Acetaminophen ..	1%
	PEG 400 ..	30%
	Ethyl alcohol ..	20%
	Water preparation for injection. ..	q.s.p. 100%

EXAMPLE 2 UP 454-21/DEXTROPROPOXYPHEN COMBINATIONS**Example 2A** Capsule (size no 1)

15	UP 454-21 ..	50 mg
	Dextropropoxyphen ..	20 mg
	Microcrystalline cellulose ..	100 mg
	Hydroxypropyl methyl cellulose ..	10 mg
	Magnesium stearate ..	5 mg
	for a capsule	

Example 2B Tablet

25	UP 454-21	50 mg
	Dextropropoxyphen ..	20 mg
	Microcrystalline cellulose	100 mg
	Lactose ..	100 mg
	Hydroxypropyl methyl cellulose ..	10 mg
	Magnesium stearate ..	5 mg
	Hydroxypropyl cellulose ..	50 mg
	for a tablet	

Example 2C Suppository

80	UP 454-21 1 00 mg	
	Dextropropoxyphen ..	40 mg
	Semi-synthetic glyceride (suppocare) ..	1880 mg
	for a suppository	

Example 2D Ophthalmic solution

40	UP 454-21 ..	0.1%
	Dextropropoxyphen ..	0.1%
	Castor oil (Cremophor EL) ..	5%
	Polysorbate 80 ..	1%
	Water preparation for injection. ..	q.s.p. 100%

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Example 3D Ophthalmic solution

5	UP 454-21	- - - - -	0 - 1 %
	Codame.	- - - - -	0 1%
	Castor oil (Cremophor EL)	- - - - -	5 %
	Polysorbate 80	- - - - -	1 %
	Water preparation for injection	- - - - -	q.s.p. 100 %

Example 3E Injectable preparation

10	LT 454-21	- - - - -	0 1%
	Codame.	- - - - -	0 1%
	PEG 400	- - - - -	30 %
	Ethyl alcohol	- - - - -	10%
	Water preparation for injection	- - - - -	q.s.p. 100 %

15 EXAMPLE 4. UP 454-21/OXYCODONE COMBINATIONS**Example 4A Capsule (size no 1)**

20	UP 454-21	- - - - -	50 mg
	Oxycodone	- - - - -	15 mg
	Microcrystalline cellulose	- - - - -	100 mg
	Hydroxypropyl methyl cellulose	- - - - -	10 mg
	Magnesium stearate	- - - - -	5 mg
	for a capsule		

25 Example 4B Tablet

30	UP 454-21	- - - - -	50 mg
	Oxycodone	- - - - -	15 mg
	Microcrystalline cellulose	- - - - -	100 mg
	Lactose	- - - - -	100 mg
	Hydroxypropyl methyl cellulose	- - - - -	10 mg
	Magnesium stearate	- - - - -	5 mg
	Hydroxypropyl cellulose	- - - - -	50 mg
	for a tablet		

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Example 4C Suppository

40	UP 454-21	- - - - -	100 mg
	Oxycodone	- - - - -	30 mg
	Semi-synthetic glyceride (suppocire)	- - - - -	1900 mg
	for a suppository		

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233What is claimed is

- 1 A pharmaceutical composition, which comprises as active principle, a combination of a cyclooxygenase-2 inhibitor and a compound selected from the group consisting of acetaminophen and the opiates.
- 2 The pharmaceutical composition according to claim 1, characterised in that the cyclooxygenase-2 inhibiting compound is (Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulphonylphenyl)methylene]dihydrofuran-2-one.
- 3 The pharmaceutical composition according to claims 1 or 2, characterised in that said opiate compound is selected from the group consisting of oxycodone, codeine and dextropropoxyphen.
- 4 The pharmaceutical composition according to claims 1 to 3, characterised in that it is presented in a form suitable for an administration via a route selected from the group consisting of the oral route, the parenteral route, the rectal route, the ocular route, the transdermal route, the nasal route, and the auricular route.
- 5 The pharmaceutical composition according to claims 1 to 4, characterised in that the weight ratio of the cyclooxygenase-2 inhibiting compound to the compound selected from the group consisting of acetaminophen and the opiates is selected in order to lead to the greater synergy between the two combined compounds, the weight ratios ranges preferentially from about 0.01 to 10, and more preferentially from 0.1 to 3.5.
6. The pharmaceutical composition according to claims 1 to 5, characterised in that it is presented as a unit dose containing from 50 mg to 200 mg of cyclooxygenase-2 inhibiting compound.

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2020
Bogotá, D C ,

Doctor
Emilio Ferrero
Apoderado

Oficio N° 1 4 9 4

ASUNTO	Radicación PCT N°	03-95518
	Trámite	011
	Evento	379
	Actuación	440
	Folios	025

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas S.A , reúne los requisitos formales exigidos por la ley al momento de su presentación

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica N° 10 de 2001


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

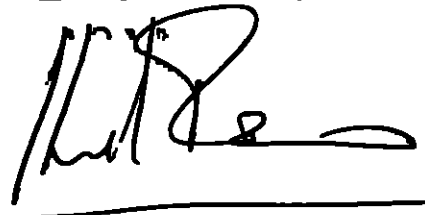
'10 FEB 2006

El anterior requerimiento fue notificado por fijación en lista de fecha, _____

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LETTER OF OPPOSITION TECHNOLOGIES SA

CANDICE ABOGADO



10 FEBRUARY 2006