Assembling the information mosaic

Donald Walter, Ph.D.
Manager, Pharma-Chem
Customer Training
Thomson Scientific
Types of Information Necessary for the Chemical Enterprise

<table>
<thead>
<tr>
<th>Research and Development</th>
<th>Product testing (clinical trials)</th>
<th>Commercial launch</th>
<th>Patent Expiry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patents</td>
<td>Product literature</td>
<td>News</td>
<td>Patent Expiry</td>
</tr>
<tr>
<td>Technical Literature</td>
<td>Regulatory</td>
<td>Commercial literature</td>
<td>Competitive Intelligence</td>
</tr>
</tbody>
</table>

**Research and Development**
- Product testing (clinical trials)
- Product literature
- Regulatory

**Commercial Launch**
- News
- Commercial literature
- Competitive Intelligence

**Patent Expiry**
- Patent Expiry
Patents
In this corner, Searle / Pfizer

- 1993-11-30 Searle (now part of Pfizer) files US application 160,594, which evolves into WO 95/15316, at least 14 related US cases, and others for a total of no less than 63 publications. Example 18 (of the WO) shows the compound now known as Celebrex (celecoxib)

  “The present invention preferably includes compounds which selectively inhibit cyclooxygenase [COX] II over cyclooxygenase I”
And in this corner, The University of Rochester

- 1995-06-07 Rochester files US application 487,752, which evolves into WO 96/40720, at least 3 related US patents and others for a total of at least 6 patent publications

  An isolated nucleic acid molecule (I) encoding human PGHS-2 (prostaglandin H synthase-2)\(^1\), is new.

  USE - The compounds isolated using the methods of (8) which inhibit prostaglandin expression, may be used to treat inflammation

- On the day that US 6,048,850 is issued, Rochester sued Searle/Pfizer for infringement

1. PGHS = COX
First-level patent data – Delphion and Micropatent

- First level patent data from USPTO, EPO, WIPO, Patent Abstracts of Japan, German Patent and Trademark Office, INPADOC, Derwent/Delphion
- Simple searching
- Easy document delivery (PDF Express)
- Extract data from various fields into comma delimited format
- Clustering to determine which patents are near each other in technology
Simple searching
Derwent

- World Patent Index, DWPI First View and Derwent Patent Citation Index
- Derwent Biotechnology Resource
- Derwent Drug File
- Derwent Geneseq
- Derwent Journal of Synthetic Methods
- Litalert
Derwent World Patent Index, First View, Patent Citation Index

- Patents from over 40 patent offices
- All bibliographic data reduced to common formats
- All abstracts in English. Since 1999, information in abstracts organized into special paragraphs
- Special indexing for chemical and electrical patents
Nucleic acid encoding human prostaglandin H synthase-2 - used in treating and detection of inflammation, pre-term labour, cancer, etc.

O'BANION, M K; WINN, V D; YOUNG, D A

(WUYR) UNIV ROCHESTER; (OBAN-I) O'BANION M K; (WINN-I) WINN V D; (YOUN-I) YOUNG D A

FDT AU-----9660293 A Based on WO-----9640720; US--2004014702 A1 Div ex US-----6048850


IC A61K-031-33; A61K-048-00; C07H-021-04; C12N-001-21; C12Q-001-26
ICS A61K-031-18; A61K-031-53; A61K-031-715; A61K-038-44; C12N-005-06; C12N-005-10; C12N-009-02; C12N-009-10; C12N-015-63; C12P-021-02; C12Q-001-02; C12Q-001-28; C12Q-001-68
An isolated nucleic acid molecule (I) encoding human PGHS-2 (prostaglandin H synthase-2), is new.

USE – The compounds isolated using the methods of (8) which inhibit prostaglandin expression, may be used to treat inflammation, e.g. arterial inflammation or pulmonary fibrosis, Alzheimer's disease, stroke or acute head injury, endometriosis, dysmenorrhea or pre-term labour. These compounds may also be used in the treatment of cancer, especially prostate cancer, colorectal cancer, squamous cell carcinoma of the head or neck, breast cancer, oral pharyngeal cancer, stomach cancer, fibrosarcoma, skin cancer or osteosarcoma. They may also be used in the treatment of radiation induced injury to the gastrointestinal tract, the brain, the lungs, haematopoietic tissue or lymphocytes (all claimed). DNA sequences complementary to (I), and antibodies immunospecific to PGHS-2 may be used in the detection of the expression of PGHS-2, and therefore in the diagnosis of the cancers listed above (also claimed). Dwg.0/11
<table>
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<tr>
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| M1 | *02* M423 M710 M760 M903 N102 N135 Q233 V754 |
| M1 | *03* M423 M720 M903 N136 N512 V802 V816 |
| M1 | *04* M423 M430 M782 M903 N102 P831 Q233 V600 V611 |
| M2 | *05* H7 H723 J0 J011 J1 J171 M226 M231 M262 M281 M320 M416 M430 M782 M903 M904 N102 P831 Q233 |
| DCN: R04038-D; R04038-M |
Derwent Geneseq

• Nucleic acid and amino acid sequences from patents from 40 patent offices
• Each sequence is described and annotated
• Bibliographic information from each patent
• Feature Tables which highlight specific areas within the sequence such as promoter regions, CAAT box, coding regions etc.
• Searchable sequences
Protein

Nucleic acid encoding human prostaglandin H synthase-2 -
used in treating and detection of inflammation, pre-term
labour, cancer, etc

IN O'Banion M K; Winn V D; Young D A
PA (UYRP) UNIV ROCHESTER.
PI WO---9640720 A1 19961219 126p
AI 1996WO-US08311 19960603
PRAI 1995US-0487752 19950607
PSL Claim 24; Page 82-84
DED 04 MAY 1997 (first entry)
DT Patent
LA English
OS 1997-052220 [05]
CR N-PSDB: AAT59634
DESC Mouse prostaglandin H synthase-2.
KW Prostaglandin H synthase-2; PGHS-2; cyclooxygenase;
inflammation; pulmonary fibrosis; Alzheimer's disease;
stroke; acute head injury; endometriosis; dysmenorrhea;
pre-term labour; prostate cancer; colorectal cancer;
squamous cell carcinoma; breast cancer; oral pharyngeal
cancer; stomach cancer; fibrosarcoma; skin cancer;
osteoarcoma; therapy; diagnosis.
ORGN Mus sp.
Mouse prostaglandin H synthase 2 (PGHS-2) (AAW12699) is responsible for increased prostaglandin synthesis associated with inflammation. Unlike PGHS-1, expression of PGHS-2 is responsive to regulatory control. The PGHS-2 amino acid sequence was deduced from a cDNA clone (AAT59634) isolated from mouse L929 cells. Transfected host cells expressing mouse or human PGHS-2 (AAW12698) can be used to identify cpds. that modulate PGHS-2 expression and activity. Cpds. that inhibit expression may be used to treat inflammation, e.g. arterial inflammation or pulmonary fibrosis, Alzheimer's disease, stroke, acute head injury, endometriosis, dysmenorrhea, pre-term labour, cancer and radiation-induced injury. Antibodies immunospecific PGHS-2 may be used to detect PGHS-2 expression, and thus in diagnosis of certain cancers.
SQL 604
SEQ

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Litalert

• Records for patent and trademark infringement lawsuits filed in the ninety-four U.S. District Courts and reported to the Commissioner of the United States Patent and Trademark Office (USPTO)
• Also included are records for thousands of lawsuits filed since the early 1970s that have never been reported in the Official Gazette.
• Each record in the database contains the patent number or trademark registration number and date of issue; patent title or trademark name; name(s) of inventors, owners, and assignees; and classification title and class number.
• Descriptive information about the specific litigation includes the court in which the action is taking place, the docket number of the class, plaintiffs and defendants, the filing date of the lawsuits, and the judgment and date, if applicable.
Method of inhibiting prostaglandin synthesis in a human host

Young Donald A - Rochester NY; O'Banion Michael K - Pittsford NY; Winn Virginia D - Rochester NY

A complaint was filed.
Technical Literature
Biosis

Subject Coverage
- Agriculture
- Anatomy
- Behavior
- Biochemistry
- Bioengineering
- Biophysics
- Biotechnology
- Botany
- Cell Biology
- Environmental Biology
- Experimental/Clinical Medicine
- Genetics
- Immunology
- Microbiology
- Pathology
- Pharmacology
- Physiology
- Toxicology

Sources
- Journals (more than 5,000)
- U.S. Patents (1986-1989, 1995 to the present)
- Reports
- Meetings (Abstracts and Papers)
- Reviews
- Books

File Data
- 1969 to the present
- More than 14,903,958 records (9/04)
- Updated four times per month
- Automatic current-awareness searches (SDIs) may be run weekly or biweekly. The default is weekly.
Concurrent treatment with renin-angiotensin system blockers and acetylsalicylic acid reduces nuclear factor kappaB activation and C-reactive protein expression in human carotid artery plaques

Author: Sattler Katherine J E; Woodrum Julie E; Galili Offer; Olson Monica; Samee Saquib; Meyer Fredric B; Zhu Xiang-Yang; Lerman Lilach O; Lerman Amir (Reprint)

Author Address: Dept Internal MedDiv Cardiovasc Dis, Mayo Clin Rochester, 200 1st St SW, Rochester, MN, 55905, USA**USA

Author E-mail Address: lerman.amir@mayo.edu


Medium: print

ISSN: 0039-2499 _(ISSN print)

Document Type: Article

Record Type: Abstract

Language: English
Abstract: Background and Purpose-The local renin-angiotensin system (RAS) and cyclooxygenase-2 contribute to the activation of nuclear factor kappaB (NFkappaB) and C-reactive protein (CRP). We hypothesized that the combination of RAS blockers (RASb) and ASA reduces NFkappaB and CRP within atherosclerotic plaques. Methods-Patients undergoing carotid endarterectomy were divided into groups according to treatment (RASb-acetyl-salicylic acid (ASA), ASA, RASb, and control). The expression of NFkappaB, CRP, and CD40L was analyzed through Western blots in the obtained plaques. Results-Plaques from patients treated with the combination of RASb and ASA showed lower expression of NFkappaB (25.4+/-9.8 densitometric units (DU)) than those of the control group (57.6+/-13.2 DU, P=0.03) as well as lower expression of CRP (20.9+/-9.6 DU) than those of the other treatment groups (ASA 86.1+/-13 DU, RASb 88.4+/-31 DU, controls 67.8+/-18.6, P=0.004). A negative expression of NFkappaB was associated with a reduced incidence of symptoms compared with a positive expression (5/33 (15.1%) versus 14/35 (40%), P=0.031). Conclusions-The combined treatment with RASb and ASA decreases the expression of inflammatory markers in atherosclerosis in humans. This study supports the role of the local RAS and cyclooxygenase-2 in the progression of atherosclerosis.
Registry Numbers: 50-78-2: acetylsalicylic acid; 329900-75-6: cyclooxygenase-2

Descriptors:
Major Concepts: Cardiovascular Medicine--Human Medicine, Medical Sciences; Enzymology--Biochemistry and Molecular Biophysics; Pharmacology

Biosystematic Names: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia

Organisms: human (Hominidae)--aged, female, male

Common Taxonomic Terms: Animals; Chordates; Humans; Mammals; Primates; Vertebrates

Diseases: carotid artery plaque {atherosclerotic plaque}--vascular disease, drug therapy, surgery

Mesh Terms: Arteriosclerosis (MeSH)

Chemicals & Biochemicals: C-reactive protein; acetylsalicylic acid--cardiovascular-drug; cyclooxygenase-2; nuclear factor kappa-B; renin-angiotensin system; renin-angiotensin system blocker--cardiovascular-drug

Methods & Equipment: Western blot--electrophoretic techniques, immunologic techniques, laboratory techniques; carotid endarterectomy--clinical techniques, therapeutic and prophylactic techniques
Concept Codes:
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
10802 Enzymes - General and comparative studies: coenzymes
11105 Anatomy and Histology - Surgery
12512 Pathology - Therapy
14506 Cardiovascular system - Heart pathology
14508 Cardiovascular system - Blood vessel pathology
22002 Pharmacology - General
22005 Pharmacology - Clinical pharmacology
22010 Pharmacology - Cardiovascular system
24500 Gerontology

Biosystematic Codes:
86215 Hominidae
### Subject Coverage

- Every subject area within the broad fields of science, technology, and biomedicine is included, such as:

<table>
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<tbody>
<tr>
<td>Agriculture</td>
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<td>Technical and Applied Sciences</td>
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<td>Zoology</td>
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### Sources

- Cover-to-cover indexing of every significant item from 5,600 leading scientific, technical, and medical journals

### File Data

- 1974 to the present
- More than 22,848,548 records (12/04)
- Updated weekly with about 14,500 records
- Automatic current-awareness searches (SDIs) are run weekly
Title: Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: Identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib)


Source: JOURNAL OF MEDICINAL CHEMISTRY 40 (9): 1347-1365 APR 25 1997

Document Type: Article

Language: English

Cited References: 39 Times Cited: 438

Abstract: A series of sulfonamide-containing 1,5-diarylpyrazole derivatives were prepared and evaluated for
Abstract: A series of sulfonamide-containing 1,5-dihydropyrazole derivatives were prepared and evaluated for their ability to block cyclooxygenase-2 (COX-2) in vitro and in vivo. Extensive structure-activity relationship (SAR) work was carried out within this series, and a number of potent and selective inhibitors of COX-2 were identified. Since an early structural lead (1f, SC-236) exhibited an unacceptably long plasma half-life, a number of pyrazole analogs containing potential metabolic sites were evaluated further in vivo in an effort to identify compounds with acceptable pharmacokinetic profiles. This work led to the identification of II (4-[(5-(4-methylphenyl)-3-[(trifluoromethyl)]-1H-pyrazol-1-yl)benzenesulfonamide, SC-58635, celecoxib), which is currently in phase II clinical trials for the treatment of rheumatoid arthritis and osteoarthritis.

Keywords Plus: NONSTEROIDAL ANTIINFLAMMATORY DRUGS; PROSTAGLANDIN-G/H SYNTHASE; ACTIVE COX-2 INHIBITORS; SELECTIVE-INHIBITION; MESSENGER-RNA; 1,2-DIARYLCYCLOPENTENES; POTENT; EXPRESSION; MECHANISM

Addresses: Penning TD (reprint author), SEARLE RES & DEV, DEPT CHEM, 4901 SEARLE PKWY, SKOKIE, IL 60077 USA
SEARLE RES & DEV, DEPT INFLAMMATORY DIS RES, SKOKIE, IL 60077 USA
SEARLE RES & DEV, DEPT MOL PHARMACOL, SKOKIE, IL 60077 USA

Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036

Subject Category: CHEMISTRY, MEDICINAL

IDS Number: WWW1b

ISSN: 0022-2623

Use the checkboxes to add compounds to the Marked Compound List.
COMPOUND SUMMARY

Use the checkboxes to add compounds to the Marked Compound List.

Compounds 1 -- 10

[Compounds images with details]

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<th>Compound Name:</th>
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**COMPOUND DATA**

**Symbol Grade Bioactivity**
- Cyclooxygenase inhibiting activity: Tested
- Enzyme inhibiting activity: Tested
- Antiinflammatory activity: Tested
Derwent Biotechnology Resource

- Biotechnology patents, technical literature and meeting reports
  - 46% journal articles,
  - 40% patents
  - 14% international conference and meeting articles.
- Genetic techniques & applications
- Bioinformatics & analysis
- Pharmaceuticals
- Therapeutics
- Diagnostics
- Disease
- Biomanufacturing & biocatalysis
- Agricultural biotechnology
- Food & food-additives
- Fuels, mining & metal recovery
- Mining & metal recovery
- Other chemicals
- Waste-disposal and bioremediation
Gene therapy with inducible nitric oxide synthase protects against myocardial infarction via a cyclooxygenase-2-dependent mechanism

Adeno virus-mediated gene transfer and expression in animal model useful for investigating gene therapy

LI QH; GUO Y; XUAN YT; LOWENSTEIN CJ; STEVENSON SC; PRABHU SD; WU WJ; ZHU YQ; BOLLI R

Univ Louisville; Johns Hopkins Univ; Genet Therapy Inc

Bolli R, Univ Louisville, Div Cardiol, Louisville, KY 40292 USA

CIRCULATION RESEARCH; (2003) 92, 7, 741-748; ISSN: 0009-7330

English; (ENG)

THERAPEUTICS-Gene Therapy; GENETIC TECHNIQUES and APPLICATIONS-Gene Expression Techniques and Analysis; GENETIC TECHNIQUES and APPLICATIONS-Transgenic Animals and Animal Models; DISEASE-Cardiovascular
IT - adeno virus-mediated human inducible nitric-oxide-synthase; beta-galactosidase reporter gene transfer; expression in host cell; Rous-sarcoma virus promoter; cyclooxygenase-2 expression profiling; mouse animal model; Western blot hybridization analysis; appl. myocardial infarction; ischemia; reperfusion injury therapy; gene therapy
- mammal enzyme EC-1.14.13.39 EC-3.2.1.23 leuko virus retro virus onco virus antiarteriosclerotic (22, 19)

DT - Literature(L)
AB - AUTHOR ABSTRACT - Although the inducible isoform of NO synthase (iNOS) mediates late preconditioning (PC), it is unknown whether iNOS gene transfer can replicate the cardioprotective effects of late PC, and the role of this protein in myocardial ischemia is controversial. Thus, the cDNA for human iNOS was cloned behind the Rous sarcoma virus (RSV) promoter to create adenovirus (Ad) 5/iNOS lacking E1, E2a, and E3 regions. Intramyocardial injection of Ad5/iNOS in mice increased local iNOS protein expression and activity and markedly reduced infarct size. The infarct-sparing effects of Ad5/iNOS were at least as powerful as those of ischemic PC. The increased iNOS expression was associated with increased cyclooxygenase-2 (COX-2) protein expression and prostanoid levels. Pretreatment with the COX-2-selective inhibitor NS-398 completely abrogated the infarct-sparing actions of Ad5/iNOS, demonstrating that COX-2 is an obligatory downstream effector of iNOS-dependent cardioprotection. We conclude that gene transfer of iNOS (an enzyme commonly thought to be detrimental) affords powerful cardioprotection the magnitude of which is equivalent to that of late PC. This is the first report that upregulation of iNOS, in itself, is sufficient to reduce infarct size. The results provide proof-of-principle for gene therapy against ischemia/reperfusion injury, which increases local myocardial NO synthase levels without the
Derwent Drug File


- All aspects of drug synthesis, development, evaluation, manufacture, and use. The highly focused coverage of the database ensures that all information retrieved is strongly drug-oriented. In addition, the unique combination of biological and chemical information enables searchers to find data on all types of structure-activity relationships.

- In addition to bibliographic information, literature records contain Derwent's abstract and extension abstract (in DRUGU only), controlled term indexing, structure codes (DRUGU only), as well as CAS Registry Numbers (R) and Enzyme Commission Numbers where applicable.

- The substance records in the registry segment contain common drug and Derwent Drug Registry names, CAS Registry Numbers, indexing terms, structure codes, and displayable and searchable structures (DRUGU only).
Accelerated atherosclerosis in inflammatory rheumatic diseases.

Haskard D O

Imperial-Coll.

London, U.K.

Scand. J. Rheumatol. (33, No. 5, 281-92, 2004) 1 Tab. 157

Ref. CODEN: SJRHAT ISSN: 0300-9742

The Eric Bywaters Centre for Vascular Inflammation, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 ONN, England. (e-mail: d.haskard@imperial.ac.uk).

LA English

DT Journal
The possible mechanisms and risk factors for accelerated atherosclerosis in rheumatic diseases are reviewed. The effects of aspirin, ibuprofen, indomethacin, diclofenac, rofecoxib, celecoxib, corticosteroids, methotrexate, hydroxychloroquine, chloroquine, simvastatin, and atorvastatin in atherosclerosis and rheumatic diseases are discussed. This review suggests that prevention of late cardiovascular complications of rheumatic diseases is an important aspect of disease management.
Derwent Drug Registry

AN  44349  DRUGU
FS  Registry
DDRN  DR9605582
DDN  CELECOXIB
RN  169590-42-5
CT  ANALGESICS;  ANTIINFLAMMATORIES;  ANTIINFLAMMATORY;  CYCLOOXYGENASE-2-INHIBITORS;  PROSTAGLANDIN-ANTAGONISTS;  CYCLOOXYGENASE-INHIBITORS
SS  ALKYLFLUORIDE;  BH-LINKED-CX;  BH-LINKED-CC;  ARYLAMINE;  PYRAZOLE;  SULFONAMIDE
Derwent Journal of Synthetic Methods

- Selective coverage of the chemical literature and patents for novel reactions
- 1 Record = 1 reaction from an article or patent
- Specially-written titles which describe the reaction in terms of the products and starting materials
- Full bibliographic data
- Derwent-written abstract which focuses on the experimental methodology for the reaction
PYRAZOLES FROM BETA-DIKETONES AND HYDRAZINES IMPROVED METHOD

Merck Frosst Canada & Co (O'Shea, P.; et al.)

W200042021

Patent

27-10

WPI 2000-482800

cf. Synth.Meth. 17, 452. This method provides an improved process for the preparation of 4-(5-phenyl-3-substituted-1H-pyrazol-1-yl)benzenesulfonamide derivatives in higher yield with a greater degree of purity than the previous processes. For further examples, see citation 1.

H Heterocyclic ring closure
Patent
Selective, preferential and partial reactions
RX(1) OF 1  A + B ===> C

RX(1)  RCT  A, 8705; 2 g
      B, 16834; 2.7 g , HCl salt
      SOL 110, DMA
      PRO C, 115207; 99% pure
      T 25.0 Cel
      TIM 16.0 hr
      CMT Water added dropwise and the mixture aged for 4 hrs. at room temp.
      CMT Path A

YIELD 85.3%
Product literature and News
Current Drugs -- IDdb

• Validated, integrated and evaluated information about the R&D portfolios of close to 18,000 companies and institutes involved in drug development including:
  – Information about more than 92,000 therapeutic patents, with optional links to the full text of the original patent.
  – Pipeline status of more than 21,000 investigational drugs, with comprehensive drug reports, development histories, bibliographies and expert commentary on the most promising candidates.
  – Over 67,000 chemical structures, fully substructure searchable for easy identification.
  – Approximately 400 meeting reports a year, from about 300 selected scientific conferences, with extensive first-time disclosure of investigational drugs.
  – A growing bibliography of more than 490,000 references, gathered from a diverse range of scientific and commercial publications, with links to abstracts of full text where available.
**Composition comprising a combination of a COX-2 inhibitor and an antioxidant - useful for the diagnosis and treatment of stroke, central nervous system disorders, ischemic stroke, Parkinson's disease and Alzheimer's disease.**

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<td>Antioxidant agent</td>
</tr>
<tr>
<td>Technologies</td>
<td>Drug combination</td>
</tr>
<tr>
<td></td>
<td>Imaging</td>
</tr>
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</table>

**Novelty**

A composition comprising a combination of a COX-2 inhibitor and an antioxidant or their isomers, salts, esters or prodrugs where the antioxidant is not melatonin is claimed, as is its use for the diagnosis and treatment of stroke. The composition is also useful for treating central nervous system disorders, ischemic stroke, Parkinson's disease, Alzheimer's disease, venous and arterial thrombosis, and may be used for diagnosing a vaso-occlusion using ultrasound and magnetic resonance direct thrombus imaging. The compounds demonstrate potent synergistic activity.

**Biology**

No biological data are presented.
Compositions of a cyclooxygenase-2 selective inhibitor and an antioxidant agent for the treatment of central nervous system disorders

Filing details: 08 June 2004
Published on: 24 February 2005
Inventors: Stephenson, Diane, T.; Taylor, Duncan, F.

Search Results
Your search for celecoxib in Drug Alerts found 53 results.

Results Summary

<table>
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</thead>
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<tr>
<td>Alerts</td>
<td>53</td>
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</table>

- **EMEA imposes restrictions on COX-2 inhibitor use.** European Agency for the Evaluation of Medicinal Products. Posted on 18th February 2005.
- **Coxib cardio risks could be class effect.** Thomson Scientific. Posted on 18th February 2005.
- **Celebrex's cardiovascular profile scrutinized.** Pfizer Inc. Posted on 23rd December 2004.
- **Pfizer reaffirms Celebrex's cardiovascular safety.** Pfizer Inc. Posted on 20th December 2004.
- **Pfizer to assess Celebrex in heart attack patients.** Pfizer Inc. Posted on 29th November 2004.
- **Cardiovascular safety concerns for Pfizer's second-generation COX-2 inhibitor.** Pfizer Inc. Posted on 13th December 2004.
- **Merck stops Vioxx derivative trial; COX-2 class scrutinized.** Thomson Scientific. Posted on 01st October 2004.
Alert based on Reference number RF585815

EMEA imposes restrictions on COX-2 inhibitor use
European Agency for the Evaluation of Medicinal Products

Press Release Posted on: 10 February 2005

Alert

The EMEA has introduced urgent interim safety restrictions on COX-2 inhibitor class drugs available in the EU, following the conclusion of the Committee for Medicinal Products for Human Use (CHMP) that the available data show an increased risk of cardiovascular adverse events.

The CHMP, which met from February 14 to 17, 2005, also concluded that the data suggested an association between duration and dose and the probability of a cardiovascular event.

Accordingly, the EMEA has stated that the COX-2 inhibitor class is contraindicated in patients with ischemic heart disease or stroke; Merck & Co Inc’s Arcoxia (etoricoxib) has also been contraindicated in patients with uncontrolled hypertension.

A warning has been given to exercise caution when prescribing this class to patients with heart disease risk factors, including hypertension, hyperlipidemia, diabetes and smoking, and in patients with peripheral arterial disease. Doctors have also been advised to prescribe the lowest effective dose for the shortest possible duration.

The committee allowed ongoing cardiovascular trials of these drugs to continue as planned, as further research in this field is needed. The finalization of the class review is expected in April 2005.

Prior to the February 2005 CHMP and FDA Advisory Committee COX-2 inhibitor meetings, a Morgan Stanley analyst suggested odds of European withdrawal of Pfizer Inc’s launched COX-2 inhibitors, Celebrex (celecoxib) and Bextra (valdecoxib), of 30 and 35%, respectively. Odds of a US withdrawal of these drugs was pegged slightly lower, at 20 and 30% respectively [585875].

Prudential Equity Group analysts have commented that although the Wall Street consensus appears to be that the FDA would not recommend withdrawal of the drugs, they had concerns that, by continuing to
Drug name: celecoxib

Originator: GD Searle & Co (Pfizer Inc)
Current partners: Yamanouchi Pharmaceutical Co Ltd
Highest Dev Status: Launched

Deals

Under the terms of this agreement, Yamanouchi was to lead the development of the compound in Japan and would collaborate with Searle to support coregistration by both companies. Yamanouchi was to pay a one-off licensing fee, make milestone payments, pay royalties and purchase compound from Searle [205479]. On March 29, 2001, an amended agreement was signed by Yamanouchi and the Japanese section of GD Searle’s parent company, Pharmacia KK. Celecoxib was to be copromoted by the two companies under a single brand name after obtaining approval in Japan. Pharmacia KK was to import the bulk drug and Yamanouchi would manufacture the finished dosage forms [404884].

Development Status detail for All Indications

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<th>Confidence</th>
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Current Drugs, SDdb

- Containing market and sales information on the top 400 pharmaceutical drugs, as well as 200 late stage drugs that are about to make a significant impact on the market, SDdb will provide unique insight into the predicted market trends from 2002 until 2007. Financial information from leading Thomson Financial products such as Worldscope Plus and First Call ensure you have the most recent and comprehensive information available. Consensus forecasts and audited sales data ensure you have accurate sales projections, current and anticipated market shares and company financial information.
Cocoxib (Celebrex), a 1,5-diarylpyrazole, is an oral selective inhibitor of inflammation-induced cyclooxygenase-2 (COX-2). It was developed and launched by GD Searle & Co (later Pharmacia Corp, now Pfizer Inc), previously in collaboration with Pfizer, and is indicated for the treatment of the signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis (OA), for the management of acute pain in adults, for the treatment of primary dysmenorrhea, and to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP) patients, as an adjunct to surgery and further endoscopic surveillance [479953]. Celebrex was first launched in the US for the RA and OA indications in January 1999 [312280], expansion of the FDA approved indications followed [479953]. By June 2000, celecoxib had been launched in the UK and Germany for the treatment of OA and RA [370012]. In July 2005, the CPMP recommended EU approval of celecoxib for the reduction of polyps in FAP patients, as an adjunct to other treatment [496124]. In December 2002, Japanese licensee Yamanouchi Pharmaceutical Co Ltd filed an NDA for cocaexib in Japan for a number of indications, including RA, OA and lower back pain [502661], [513094], with approval expected during 2004 [536552]. The company was still awaiting Japanese approval in January 2005 [584044]. In December 2004, the FDA requested that Pfizer suspend all DTC advertising and change the information provided to physicians to reflect FDA recommendations that physicians consider alternative therapies, whilst the FDA evaluate findings of a potential increase in risk of cardiovascular adverse events in patients taking cocaexib [577516]. In October 2004, Pfizer announced that it would fund a 4000-patient study to assess the effects of cocaexib on inflammation and cardiovascular events in OA patients who had had a recent heart attack [564947]. In February 2005, the FDA’s advisory committee voted that cocaexib should continue to be marketed in the US [587050]; the EMEA also released an update on the safety of COX-2 inhibitors following a review of the cardiovascular data, with no major changes to existing advice. Finalization of the class review was expected in April 2006 [587093].
Postmarketing studies

In December 2004, Pfizer reported that one of two long-term anticancer studies, the Adenoma Prevention with Celecoxib (APC) trial, had been suspended pending further investigation into findings that patients showed a 2.5-fold increase in risk of experiencing a major fatal or non-fatal cardiovascular event compared to those patients taking placebo; the Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial showed no increased risk of cardiovascular events in patients taking celecoxib compared with placebo and was ongoing in December 2004 [576700].

Analyst commentary

Following the FDA Advisory Committee meeting in February 2005, analysts at Prudential Equity Group rated the outcome as largely as expected for Pfizer; analysts expect celecoxib will stay on the market, but with strong label revisions likely, along with limited marketing practices allowed [586572], [586571], [586570].

Classification

**SDdb franchise:** COX-2 inhibitors

**EphMRA:** Gynaecological antispasmodics, All other antineoplastics, Coxibs, Non-narcotics and anti-pyretics, Anti-Alzheimer products

**Mode of Action:** Anticancer; Analgesic; Non-steroidal anti-inflammatory; Nootropic agent; Cylooxygenase 2 inhibitor

Launch and Patent Expiry

**First launch date:** Jan 01 1999 (US)

**Patent expiry (est.):** Nov 30 2013 (US-05466823)

Sales and Market Share

**Sales in USD (millions): celecoxib**

[Graph showing sales in USD millions for different companies]
Sales in USD (millions): celecoxib

Sales comment

Sales forecast data for Pfizer Inc and Yamanouchi Pharmaceutical Co Ltd have been obtained from analyst reports published in the 2004 period. This product was part of the Pharmacia Corp portfolio prior to the Pfizer acquisition; therefore, sales for 2002 have been attributed to Pharmacia and sales for subsequent years have been attributed to Pfizer. Data presented are based on analyst opinion published prior to the withdrawal of Merck & Co Inc's rofecoxib (Vioxx; cv) in September 2004 and therefore do not reflect the impact of this event on the forecast sales of this drug, or indeed the impact of the FDA advisory committee recommendations in February 2005.

Pfizer's sales of celecoxib (Celebrex) for 2003 were $1.883 billion, and were in-line with or above analyst forecasts [527516], [633335], [633472]. Although analysts forecast growth for celecoxib in select markets, such as Japan, future overall sales of celecoxib for Pfizer are predicted to be cannibalized by valdecoxib (Bextra; cv) [563344]. Analysts suggest that launch in Japan may not occur until 2005 [576384], [576388], [580713].

Market share 2002 vs 2007 (Franchise: COX-2 inhibitors)
Market share 2002 vs 2007 (Franchise: COX-2 inhibitors)

Total reported sales, 2002 USD (millions): 6980

Total forecast sales, 2007 USD (millions): 7527

Regional Analysis

United States

Therapeutic uses (Source: DRUGDEX® System, MICROMEDEX)

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<td>-</td>
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<td>no</td>
<td>effective</td>
<td>-</td>
</tr>
<tr>
<td>PAIN - ACUTE</td>
<td>yes</td>
<td>no</td>
<td>effective</td>
<td>-</td>
</tr>
</tbody>
</table>

• Celecoxib may be useful in the management of the symptoms of systemic lupus erythematosus
• Hastened improvement in schizophrenia symptoms when used as add-on therapy with risperidone
• Celecoxib was effective in patients with rheumatoid arthritis, in controlled studies
• Significant pain relief after 1 to 2 weeks, in controlled studies
• Celecoxib is indicated for the treatment of acute pain including PRIMARY DYSMENORRHEA
Current Drugs, IDeals

• Business intelligence tool for Licensing and New Business Development Executives
Salix and ALTANA to copromote XIFAXAN
Salix Pharmaceuticals Ltd, 4th March 2005

Salix Pharmaceuticals Ltd and ALTANA Pharma US Inc are to copromote the oral antibiotic XIFAXAN (rifaximin) for the treatment of travellers diarrhea.

"This copromotion will allow Salix to continue to focus its sales efforts on its primary target audience - gastroenterologists - while at the same time allowing ALTANA Pharma the opportunity to expand the XIFAXAN market by generating exposure to its target audience - primary care physicians," said Carolyn Logan, President and CEO of Salix.[588198]

Pharmacopoeia enters inflammation pact with Celgene
Pharmacopoeia Inc, 4th March 2005

Pharmacopoeia Inc has entered into a research collaboration with Celgene Corp. The companies will work together to identify small molecule lead compounds suitable for further development as anti-inflammatory agents.

Pharmacopoeia will provide its small molecule discovery expertise in identifying leads against a selected Celgene target. Pharmacopoeia will receive funding for providing these research activities and will be entitled to receive additional payments upon the successful achievement of milestones and royalties upon the commercialization of any drugs emanating from this relationship.[477845]

AME to optimize anti-IL-9 antibody for MedImmune
Applied Molecular Evolution Inc, 4th March 2005

Applied Molecular Evolution Inc (AME) has initiated the optimization of an antibody against IL-9 for MedImmune Inc as a part of the companies' alliance to optimize four monoclonal antibodies.
Regulatory
Liquent IDRAC

- Database services that provide information and rules and regulations for registering new drugs in 41 jurisdictions around the world.
Search Results for Terms: cyclooxygenase

Topic Matches (All Regions)

No matches found.

IDRAC Title Matches

No matches found.

Full Text Matches


2. Drug Approval Package: Celebrex (Celecoxib) - Approval Letter, Labeling, Reviews
   (Medical, Chemistry, Pharmacology, and Clinical Pharmacology Biopharmaceutics),
   Administrative Documents and Correspondence, 23-Dec-1999
   IDRAC Number: 23560. Abstract not available

Precautions, p.11ff

**Center for Drug Evaluation and Research**

**Approval Package for**

Celebrex (Celecoxib) Capsules

Company: G.D. Searle & Co.

Application No.: 21-156 & 20998/3007

Approval Date: 12/23/99

---

**Renal Effects:** Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

Caution should be used when initiating treatment with CELEBREX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS: Advanced Renal Disease).

**Hematological Effects:** Anemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anemia was 0.0% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES: Special Studies: Platelets).

**Fluid Retention and Edema:** Fluid retention and edema have been observed in some patients taking CELEBREX (see ADVERSE REACTIONS). Therefore, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure.

**Preexisting Asthma:** Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe
This Warning Letter concerns Merck & Co. Inc.’s (Merck) promotional activities and materials for the marketing of Vioxx (rofecoxib) tablets. Specifically, we refer to promotional audio conferences given on behalf of Merck by Peter Holt, MD, a press release, and oral representations made by Merck sales representatives to promote Vioxx. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and applicable regulations. See 21 U.S.C. §§ 331(a) and (b), 352(a), (f), and (n), and 355 (a).

You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresents the safety profile for Vioxx. Specifically, your promotional campaign discounts the fact that in the VIGOR study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal antiinflammatory drug (NSAID), Naprosyn (naproxen).
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# Code of Federal Regulations

## CFR Index > Title 21 - Food and Drugs

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| **2. CFR 21 CFR 100.169** | PDF    | $49.00 | ORDER | Download      |
| 01-Apr-2004              |        |       |       |               |
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| Product Type: Standard   | | | | | |

| **3. CFR 21 CFR 1300-END** | PDF    | $30.00 | ORDER | Download      |
| 01-Apr-2004              |        |       |       |               |
| Code of Federal Regulations - Title 21 Part 1300-END - Food and Drugs (Drug Enforcement Admin.) | | | | | |
| Product Type: Standard   | | | | | |

| **4. CFR 21 CFR 170.199** | PDF    | $50.00 | ORDER | Download      |
| 01-Apr-2004              |        |       |       |               |
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| Product Type: Standard   | | | | | |
Standard
Code of Federal Regulations - Title 21 Part 300 - Part 499 - Food and Drugs (FDA-Drugs for Human Use)
Document Number: CFR 21CFR 300-499
Code of Federal Regulations
01-Apr-2004
377 pages

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- Special orders and age-dated materials are not returnable.
- Shipping charges for non-PDF items will be added to your total based on the shipping method that you choose.
Commercial literature
Newport Strategies

• Vision CI
  – Newport Vision CI provides critical, early intelligence and independent analysis to help identify and assess early signs of generic competition and monthly updates to follow generic developments

• Vision Sourcing
  – Research, identify, and evaluate API manufacturers with specific product offerings, technical capabilities, or strategic partnerships
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<td>PFIZER</td>
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<td>Analgesic, Anti-Inflammatory (Nonsteroidal), Cyclooxygenase-2 Inhibitor</td>
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Filter by country: **USA**
### celecoxib

**Sales by Dose Form:**
- celecoxib Sales (in $USD):
  - USA: $2,596.7M, $2,457.5M
  - EU: $463.2M, $396.9M
  - Rest of Europe: $33.8M, $33.1M
  - Rest of World: $343.3M, $304.4M
  - Worldwide: $3,437.1M, $3,191.9M

**Merck Therapeutic Index:**
- Analgesic
- Anti-inflammatory (Nonsteroidal)
- Cyclooxygenase-2 Inhibitor

**EphMRA Therapeutic Index:**

**Newport Analysis**
- **API Availability Status:**
  - No Confirmed Sources
  - Excessively Available
  - Excessively Available
- **US Generic Forecast:**
  - Delayed
  - Highly Competitive

**Patents & Exclusivities**
- The 1st patent expiry in USA is a(n) Composition patent with an expiry date of 30 Nov 13. Patent Number 5563165.
- The 2nd patent expiry in USA is a(n) Method of use patent with an expiry date of 30 Nov 13. Patent Number 5753688.
- The 3rd patent expiry in USA is a(n) Product patent with an expiry date of 30 Nov 13. Patent Number 5510408.
celecoxib

View Orange Book Info

Launched Drug Forms: Detail [✓] save to Excel

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View IMS Info

US Orange Book Approved Drug Forms [Show Product Family] [✓] save to Excel

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Trimax Express

Trimax Express
Chennai, Tamil Nadu, India

Group Type: Dose
Number of US DMFs: 0
Number of Active US DMFs: 0
Number of EEC COS: 0
Number of APIs: 0
Dose Product Count: 57

US FDA Warning Letters:

Dose Forms Launched: Nasal, Oral, Other, Topical
Markets served: Israel, Singapore, Taiwan, Thailand

Trimax Express Products by Therapeutic Category by Market

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Competitive Intelligence
Patent literature lends itself to automated tools

- Delphion – Mapping tools
- Derwent Analytics on Vantage Point software
- Micropatent – Aureka
- STN Express
Delphion

Clustering to determine which patents are near each other in technology
## Derwent Analytics on Vantage Point

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Which company is active in which fields?

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- **A61K** Preparations for medical, dental, or toilet purposes
- **A61P** Therapeutic activity of chemical compounds or medicinal preparations
- **C07C** Acyclic or carbocyclic compounds
- **C07D** Heterocyclic compounds
- **C12N** Micro-organisms or enzymes; compositions thereof; propagating, preserving, or maintaining micro-organisms; mutation or genetic engineering; culture media
- **C12Q** Measuring or testing processes involving enzymes or micro-organisms; compositions or test papers therefor; processes of preparing such compositions; condition-responsive control in microbiological or enzymological processes
How close are the companies’ work?
Thank you

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Don.Walter@Thomson.com
http://www.thomsonscientific.com

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  Whitney Museum of American Art, New York
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