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Treatment of Pain

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Abstract

This issue of **Drugs of the Future** features the *Annual Review* dedicated to updated information on drugs for the treatment of pain. The following table lists 94 drugs under development in this area, including those drugs that have been published in previous issues of the journal and others in preparation for publication in the journal, as well as some drugs that have been launched for an indication other than that discussed in the review. Information on the following 17 products has been updated in this issue: ajulemic acid, capsavanil, celecoxib, devazepide, eletriptan, etoricoxib, frovatriptan, lamotrigine, levetiracetam, memantine hydrochloride, oxcarbazepine, parecoxib sodium, pregabalin, rhenium Re-186 etidronate, venlafaxine hydrochloride, ziconotide and zonisamide.

We would like to remind the readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

Annual Review 2002: Treatment of Pain

Drug	Source	Description/Indication	Phase
ABT-594[1]	Abbott	Non-opioid analgesic	II
		Neuropathic pain	II
ABT-963	Abbott	Analgesic	I
ADL-10-0101	Adolor	Opioid analgesic	II
ADL-10-0116	Adolor	Opioid analgesic	I
AERx Morphine Sulphate	Aradigm	Opioid analgesic	II
Ajulemic Acid[1]	Atlantic Technology Ventures	Neuropathic pain	II
ALX-0646	NPS Allelix	Antimigraine	II
AM-336	Amrad	Non-opioid analgesic	I/II
Aminoacetic Acid	AstraZeneca	Neuropathic pain	I
Aminophylline Hydrate[2]	Epitome	Antimigraine	II
APF-112	A.P. Pharma	Analgesic	I
Aquavan	ProQuest/Guilford	Intravenous anesthetic	I
Asimadoline	Merck KGaA	Opioid analgesic	II
BIBN-4096BS	Boehringer Ingelheim	Antimigraine	II
BMS-347070	Bristol-Myers Squibb	Non-opioid analgesic	II
Botulinum Toxin Type B	Elan	Antimigraine	II/III
Capsavanil[1]	Dong-A	Neuropathic pain	II
Carabersat	GlaxoSmithKline	Antimigraine	II
Celecoxib[1,2]	Pfizer	Non-opioid analgesic	R-2001
Cizolirtine Citrate	Esteve	Non-opioid analgesic	II
CJC-1008	ConjuChem	Opioid analgesic	II
		Neuropathic pain	II
CNS-5161	Cambridge NeuroScience	Neuropathic pain	II
Contulakin G	Cognetix	Non-opioid analgesic	III
COX-189	Novartis	Analgesic	III
DepoMorphine	SkyePharma	Opioid analgesic	III
Devazepide[1]	ML Labs./Panos Therapeutics	Neuropathic pain	II
Dexmedetomidine Hydrochloride[1,2]	Abbott	Non-opioid analgesic	Prereg
DPI-3290	Ardent Pharmaceuticals	Opioid analgesic	II
Dronabinol[2]	GW Pharmaceuticals	Antimigraine	I
		Cancer pain	II
Dronabinol/Cannabidiol	GW Pharmaceuticals	Neuropathic pain	II
DUROS-Sufentanil	Durect	Analgesic	III
E-5296	Esteve	Opioid analgesic	I
E-6087	Esteve	Non-opioid analgesic	I
Eletriptan[1]	Pfizer	Antimigraine	L-2001
EpiCept NP1 Cream	EpiCept	Analgesic	I/II
Erlosamide	Schwarz	Neuropathic pain	II
Esterom	Entropin	Analgesic	III
Etoricoxib[1]	Merck & Co.	Analgesic	L-2002
E-TRANS™-Fentanyl	Alza	Opioid analgesic	III
Frakefamide	Shire BioChem	Opioid analgesic	II
Frovatriptan[1]	GlaxoSmithKline/Vernalis	Antimigraine	Reg-2000
GPI-5693	Guilford	Neuropathic pain	I
GW-406381	GlaxoSmithKline	Analgesic	I
GW-468816	GlaxoSmithKline	Prophylaxis of migraine	I
GW-493838	GlaxoSmithKline	Neuropathic pain	I
HP-228	Lion Bioscience	Analgesic	II
HydrocoDex	Endo	Analgesic	II
Hydrocodone/Acetaminophen/Naltrexone	Pain Therapeutics	Opioid analgesic	II
JTC-801	Japan Tobacco	Analgesic	II
Ketoprofen[2]	Wyeth Pharmaceuticals	Non-opioid analgesic	III
		Antimigraine	III
Lamotrigine[1,2]	GlaxoSmithKline	Neuropathic pain	II
Levetiracetam[1,2]	UCB	Neuropathic pain	L-2000
LidoPAIN HM[3]	EpiCept	Antimigraine	II
Memantine Hydrochloride[1,2]	Forest/Neurobiological Technologies	Neuropathic pain	III
Metoclopramide Hydrochloride/ Naproxen Sodium	Pozen	Antimigraine	III
MorphiDex	Endo	Opioid analgesic	III

Continuation

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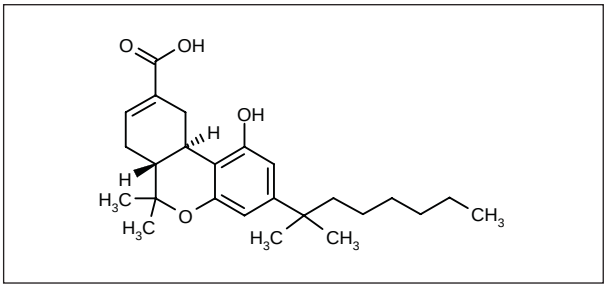
Drug	Source	Description/Indication	Phase
Morphine Hydrochloride	Shionogi	Opioid analgesic	L-2001
Morphine/Naloxone	Pain Therapeutics	Opioid analgesic	II
Morphine-6-Glucuronide	CeNeS/Elan	Opioid analgesic	II
MorViva	Pain Therapeutics	Cancer pain	II
MT-400	Pozen	Antimigraine	II
MT-500	Pozen	Prophylaxis of migraine	I
Nitronaproxen	NicOx/AstraZeneca	Non-opioid analgesic	II
NO-Paracetamol	NicOx	Non-opioid analgesic	I
OMS-103HP	Omeros	Anagelsic	II
ONO-8922	Ono	Non-opioid analgesic	I
ORG-25435	Organon	Anesthetic	I
Oxcarbazepine[1,2]	Kissei	Neuropathic pain	II
OxycoDex	Endo	Analgesic	II
Oxycodone Hydrochloride/Ibuprofen	Forest	Analgesic	Prereg
Oxycodone/Naloxone	Purdue Pharma	Analgesic	I
OxyTrex	Pain Therapeutics	Opioid analgesic	I/II
Parecoxib Sodium[1]	Pharmacia	Analgesic	L-2002
PercoDex	Endo	Analgesic	II
Powder Ject Lidocaine	AlgoRx/Celltech	Local anesthetic	II
Pregabalin[1]	Pfizer	Neuropathic pain	III
Propiram Fumarate	Roberts	Opioid analgesic	III
Prosaptide TX14(A)	Bio-Technology General	Neuropathic pain	II
ReN-1869	Novo Nordisk/ReNeuron	Neuropathic pain	II
Rhenium Re-186 Etidronate[1]	Mallinckrodt	Cancer pain	Prereg
RS-127445	Roche Bioscience	Antimigraine	I
S-8117	Shionogi	Cancer pain	Prereg
Sarpogrelate Hydrochloride[1,2]	Mitsubishi Pharma	Analgesic	II
Sn117m-DTPA	Berlex/Diatide	Cancer pain	II
SR-144190	Sanofi-Synthélabo	Non-opioid analgesic	I
Tetrodin	International Wex Technologies	Non-opioid analgesic	I
Tilmacoxib[1]	Japan Tobacco	Non-opioid analgesic	II
Tramadol Hydrochloride/Naltrexone	Pain Therapeutics	Opioid analgesic	II
Ultracet	Ortho-McNeil	Analgesic	L-2001
VANH-36	Vita-Invest	Analgesic	I
Venlafaxine Hydrochloride[1,2]	Wyeth Pharmaceuticals	Neuropathic pain	II
ZD-6416	AstraZeneca	Non-opioid analgesic	II
Ziconotide[1]	Elan	Non-opioid analgesic	III
		Neuropathic pain	III
Zonisamide[1,2]	Draxis Health	Prophylaxis of migraine	III
		Neuropathic pain	II

[1]Previously published in Drugs of the Future. [2]Launched for another indication. [3]Launched for the treatment of neuropathic pain.

Ajulemic Acid



Ajulemic acid, or CT-3, is a synthetic, chirally pure derivative of carboxylic tetrahydrocannabinol, the active ingredient in marijuana, designed to have increased analgesic and antiinflammatory properties and reduced psychotropic activity compared to the parent compound. It is being developed by Atlantic Technology Ventures for the treatment of chronic pain and inflammation associated with a variety of disease states and other severe diseases, including neurological, musculoskeletal and gastrointestinal disorders, multiple sclerosis, glaucoma and cancer.

Preliminary studies have shown that ajulemic acid demonstrates analgesic/antiinflammatory properties at microgram doses without CNS or gastrointestinal adverse effects, and that it reduces joint damage caused by rheumatoid arthritis. CT-3 has also been evaluated in rats with local irritation and inflammation of nervous tissue induced by PAF injection into the hindpaw. CT-3 not only fully reversed PAF-induced allodynia but also increased the pain threshold beyond the normal level. Atlantic has successfully completed a phase I clinical trial for CT-3 and recently received the green light from the German authorities to initiate a phase II pilot trial for chronic neuropathic pain. The randomized, double-blind, placebo-controlled, dose-escalating, crossover trial will enroll 21 patients at the University of Hannover Medical School. The company intends to develop oral and parenteral formulations of the compound (1, 2).

Atlantic Technology Ventures has entered into a research agreement with the Pain Management and Research Center, part of the Royal North Shore Hospital of the University of Sydney, with the aim of investigating the synergistic effects of opioids and cannabinoids, specifically CT-3. Human and animal studies indicate that marijuana- and cannabis-related drugs have analgesic properties that synergistically enhance the pain-relieving action of opioids. The goal of a combination treatment with opioids and cannabinoids is to significantly reduce the amount of opioids required for a specific therapeutic effect, thereby decreasing any opioid-related adverse effects. As part of the research, CT-3 will be studied in models of chronic pain, particularly with reference to neuropathic pain. The analgesic activity of CT-3 in normal animals and those with nerve injury-induced neuropathic pain, in addition to the cellular actions and intracellular systems which mediate the cellular actions of CT-3, will be studied. Specifically, scientists will seek to identify any mixed cannabinoid/nonsteroidal antiinflammatory drug (NSAID) actions of CT-3 that might provide relief in both chronic and acute pain states (3).

Ajulemic acid has also shown antispastic activity in an animal model of multiple sclerosis at a dose level achievable in humans. In the study at the Institute of Neurology, University College London, CT-3 produced a significant decrease in spasticity, rapid inhibition of limb stiffness and a relatively long-lasting effect. The data indicated that the tested dose achieved near-maximal inhibition of spasticity. CT-3 appeared to be 100 times more potent in relieving the symptoms of tremor and spasticity than other cannabinoids such as tetrahydrocannabinol and cannabidiol. The data from the study validate spasticity as a potential indication for CT-3 (4).

1. *Go-ahead for phase II pilot study of CT-3 in chronic neuropathic pain*. DailyDrugNews.com (Daily Essentials) May 3, 2002.

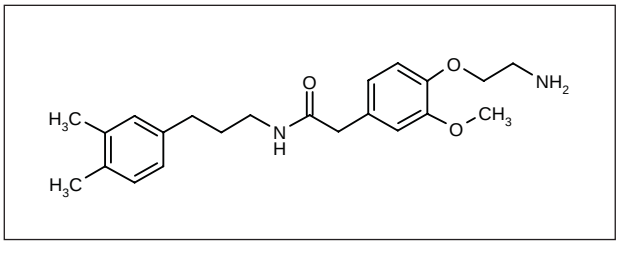
2. *U.S. Army to test CT-3 in vivo*. DailyDrugNews.com (Daily Essentials) May 21, 2001.

3. *Synergies between CT-3 and opioids to be studied*. DailyDrugNews.com (Daily Essentials) May 31, 2001.

4. *CT-3 shows antispastic activity in animal model of MS*. DailyDrugNews.com (Daily Essentials) May 8, 2002.

Original monograph - Drugs Fut 2001, 26(4): 342.

Capsavanil



Dong-A Pharmaceuticals is conducting phase II clinical studies with capsavanil (DA-5018, KR-25018), a nonopioid capsaicin derivative, for the treatment of pain associated with osteoarthritis (1).

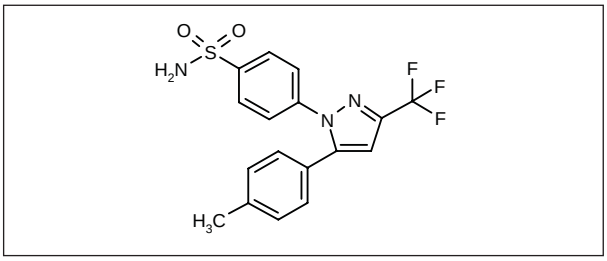
Examination of vehicle systems allowing transdermal permeation of DA-5018 indicated that a binary system is the best approach, with the combination of ethoxydiglycol and isopropyl myristate yielding the maximum flux for DA-5018 across intact skin in mice (2).

1. *DA-5018 development status*. Korea Research Institute of Chemical Technology Company Communication 2000, Nov 30.

2. Cha, B.J., Lee, E.D., Kim, W.B., Chung, S.J., Lee, M.H., Shim, C.K. *Enhanced skin permeation of a new capsaicin derivative (DA-5018) from a binary vehicle system composed of isopropyl-myristate and ethoxydiglycol*. Arch Pharmacal Res 2001, 24(3): 224.

Original monograph - Drugs Fut 2000, 25(11): 1131.

Celecoxib



The use of celecoxib (Celebrex®) for the management of acute pain and primary dysmenorrhea in adults was approved late last year by the FDA. Celecoxib, comarketed by Pharmacia and Pfizer, is the only COX-2-specific inhibitor approved to date for both osteoarthritis and adult rheumatoid arthritis and the relief of pain. It has also been approved for reducing the number of adenomatous colorectal polyps in familial adenomatous polyposis as an adjunct to standard care (1).

In a randomized, placebo-controlled study, 30 patients with osteoarthritis undergoing knee surgery were given either celecoxib or diclofenac from 24 h before to 5 days after surgery. Both drugs exhibited analgesic activity compared to placebo. Cyclooxygenase type 2 was associated with prostaglandin generation, and COX-2 inhibition appeared to be a valid method of achieving analgesia in this setting (2).

Celecoxib 200 mg b.i.d. was compared with naproxen 500 mg b.i.d. in 202 patients with acute shoulder pain in a randomized, double-blind, multicenter study. Treatments were administered for 14 days. Both celecoxib and naproxen demonstrated similar efficacy in decreasing pain (3).

A review has been published discussing the human pharmacokinetics, clinical pharmacology and toxicities of celecoxib and rofecoxib in the management of acute and chronic orofacial pain. The antiinflammatory and analgesic effects and safety profiles of the agents are discussed. It was concluded that both compounds are suitable for use in dental practice (4).

Celecoxib treatment was evaluated in 67 patients who had not tolerated NSAIDs and who had pseudoallergic reactions to nimesulide, acetaminophen or both. Patients received placebo followed 24 h later by a cumulative dose of celecoxib of 100 mg. After 48 h, a cumulative celecoxib dose of 200 mg was administered. Celecoxib was safe and well tolerated in these patients (5).

Two randomized, double-blind, placebo-controlled tolerability studies were conducted to evaluate daily doses of rofecoxib of 12.5 and 25 mg (10 patients) and daily doses of celecoxib of 100-200 mg (14 patients) in patients with aspirin-induced asthma. Both treatments were found to be well tolerated by this clinically stable population (6).

Two randomized, double-blind, multicenter, placebo-controlled trials evaluated single- and multiple-dose administration of celecoxib for the treatment of pain after orthopedic surgery in a total of 418 patients. During the single-dose assessment period (SDAP) of the trials, a single oral dose of celecoxib 200 mg, hydrocodone 10 mg/acetaminophen 1000 mg or placebo was administered within 24 h after the end of anesthesia. In the multiple-dose assessment period (MDAP), those patients receiving no rescue medication or only 1 dose of rescue medication in the following 8 h continued on study medication t.i.d. for up to 5 days. In the SDAP, celecoxib and hydrocodone/acetaminophen provided similar analgesia, whereas celecoxib t.i.d. was more effective and better tolerated than hydrocodone/acetaminophen t.i.d. in the MDAP (7). The results of this study and some of those that follow are summarized in Table I.

A randomized, placebo-controlled study was designed to compare rofecoxib 50 mg, celecoxib 200 and 400 mg, ibuprofen 400 mg and placebo in 482 patients with acute postoperative dental pain. The analgesic efficacy of rofecoxib 50 mg was significantly greater than both doses of celecoxib (8).

Researchers conducting a randomized, double-blind, placebo-controlled study assigned 112 outpatients undergoing ENT surgery to placebo, acetaminophen 2 g, celecoxib 200 mg or celecoxib 200 mg plus acetaminophen 2 g for the treatment of pain. While celecoxib alone and acetaminophen alone produced results similar to placebo, the combination of celecoxib and acetaminophen significantly reduced postoperative pain compared with placebo (9).

Three case reports of patients with hemicrania continua successfully treated with specific COX-2 inhibitors have been reported. Currently, the only available treatment for this disorder is indomethacin, but its long-term use is often limited by side effects. The COX-2 inhibitors celecoxib and rofecoxib were tried in 3 patients either

Table I: Clinical studies of celecoxib (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Arthralgia	Randomized, double-blind, multicenter	Celecoxib, 200 mg bid po (n=99) Naproxen, 500 mg bid po (n=103)	202	Preliminary results showed that efficacy of celecoxib was similar to naproxen in patients with acute shoulder pain	3
Pain	Randomized, double-blind, multicenter, pooled data	Celecoxib, 200 mg sd po (n=141) → (8 h later and ≤ 1 dose rescue drug) Celecoxib, 200 mg tid po x 5 d (n=185) Hydrocodone/acetaminophen, 10/1000 mg sd po (n=136) → (8 h later and ≤ 1 dose rescue drug) Hydrocodone/acetaminophen, 10/1000 mg tid po x 5 d (n=181) Placebo (n=141) → (8 h later and ≤ 1 dose rescue drug) Celecoxib or hydrocodone/acetominophen	418	Celecoxib 200 mg sd had the same tolerability and efficacy as hydrocodone/acetaminophen 10/1000 mg in the treatment of orthopedic postoperative pain, but over a 5-day period, celecoxib tid had greater analgesic efficacy than hydrocodone/acetaminophen tid	7
Pain	Open, randomized	Rofecoxib, 50 mg sd po (n=151) Celecoxib, 200 mg sd po (n=90) Celecoxib, 400 mg sd po (n=151) Ibuprofen, 400 mg sd po (n=45) Placebo (n=45)	482	Rofecoxib 50 mg had significantly greater analgesic efficacy than celecoxib 200 and 400 mg in patients with acute dental pain	8
Postoperative pain	Randomized, double-blind	Acetaminophen, 2 g po Celecoxib, 200 mg po Celecoxib/acetaminophen, 200 mg/2 g po Placebo (Vitamin C, 500 mg) po	112	Celecoxib was not effective when administered as a single dose for preventing analgesia in patients undergoing ENT surgery, but it was effective in combination with acetaminophen in decreasing postoperative pain	9
Migraine	Open	Celecoxib, 600-800 mg/d Rofecoxib, 75-150 mg/d	3	Preliminary results showed that celecoxib and rofecoxib appear to be effective in patients with hemicrania continua at doses higher than those usually prescribed	10

experiencing incomplete pain relief or side effects on indomethacin. The results showed that both celecoxib and rofecoxib could provide complete pain relief, although at higher doses than those normally prescribed (10).

A method for fast relief of pain comprising the oral administration of celecoxib has been claimed (11).

Combinations of a selective COX-2 inhibitor and a vasomodulator have been found to be useful for the treatment of generalized or headache pain. Preferably, the COX-2 inhibitor is celecoxib (12).

A method for the treatment or prevention of chronic prostatitis or chronic pelvic pain syndrome containing a COX-2 inhibitor has been claimed. Exemplified COX-2 inhibitors are celecoxib, parecoxib, rofecoxib, valdecoxib, meloxicam, flosulide, nimesulide, etoricoxib, NS-398, DUP-697, SC-58125, SC-58635 and RS-57067 (13).

1. *Celebrex indications expanded with recent FDA approval*. DailyDrugNews.com (Daily Essentials) Nov 6, 2001.

2. Harte, B.H., Murphy, F.M., Conway, F.M., Quinian, W.R., Cunnigham, A.J., Fitzgerald, D.J. *The effects of selective cyclo-oxygenase-2 inhibition on postoperative analgesia and prostaglandin formation*. Eur J Anaesthesiol 2001, 18(Suppl.): 140.

3. Bertin, P., Behier, J.M., Noel, E., Leroux, J.L., Herman, H., Jolchine, I. *Efficacy of celecoxib in patients with acute shoulder pain: Randomized double-blind comparison with naproxen*. Annu Eur Congr Rheumatol (June 13-16, Prague) 2001, Abst SAT0115.

4. Moore, P.A., Hersh, E.V. *Celecoxib and rofecoxib – The role of COX-2 inhibitors in dental practice*. J Am Dent Assoc 2001, 132(4): 451.

5. Dama, A.R., Liccardi, G., Lobefalo, G., Bonadonna, P., Schiappoli, M., Crivellaro, M., Senna, G. *Celecoxib, a new selective COX 2 inhibitor, is a safe alternative drug in highly NSAIDs-intolerant patients*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 411.

6. Vaghi, A., De Bernardi, G., Grassi, N., Capato, S., Cicchitto, G., Sestini, P., Robuschi, M., Bianco, S. *Tolerance of two COX2 inhibitors, rofecoxib and celecoxib, in aspirin sensitive asthmatics*. Eur Respir J 2001, 18(Suppl. 33): Abst P2884.

7. Gimbel, J.S., Brugger, A., Zhao, W., Verburg, K.M., Geis, G.S. *Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults*. Clin Ther 2001, 23(2): 228.

8. Fricke, J.R., Malmstrom, K., Kotey, P., Kress, B., Sperling, R.S., Morrison, B. *Rofecoxib compared to celecoxib for the treatment of post-op dental pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 801.

9. Issioui, T., Klein, K.W., White, P.F., Thornton, K.C., Coloma, M. *Efficacy of celecoxib and acetaminophen alone and in combination for preventing postoperative pain*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-36.

10. Rozen, T.D. *Treatment of hemicrania continua with high dose celecoxib and rofecoxib*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P06.115.

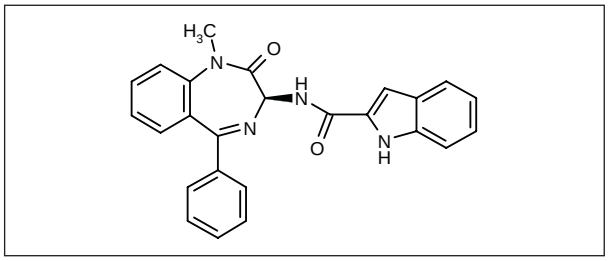
11. Karim, A. et al. (Pharmacia Corp.) *Use of a celecoxib compsn. for fast pain relief*. WO 0191750.

12. Hassan, F., Forbes, J.C. (Pharmacia Corp.). *Selective cyclooxygenase-2 inhibitors and vasomodulator cpds. for generalized pain and headache pain*. WO 0205799.

13. Nickel, C.J. et al. (Merck & Co., Inc.). *Method for treating or preventing chronic prostatitis or chronic pelvic pain syndrome*. WO 0115687.

Original monograph - Drugs Fut 1997, 22(7): 711.

Devazepide



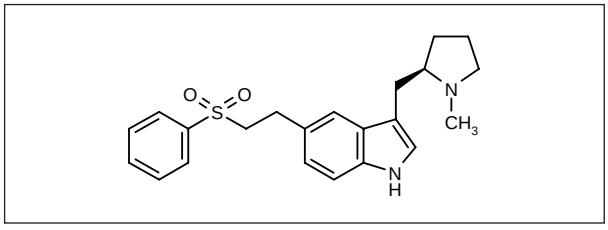
Devazepide (Devacade®) is a selective cholecystokinin CCKA (CCK1) receptor antagonist and the first orally administered product in this class of compounds specifically targeted for neuropathic pain, offering a new way of treating this type of pain.

Preliminary positive results from ML Laboratories' phase II clinical trial of devazepide in patients suffering from neuropathic pain were confirmed by completion of the analysis of the data relating to all participating patients. In this study, 40 patients with moderate to severe neuropathic pain were administered 2 strengths of devazepide or placebo in addition to their existing opioid and other analgesic therapy. During treatment with devazepide at the higher dose, 50% of patients reported significantly improved pain relief compared to their current therapy, with no reports of severe side effects. The significant pain-relieving action of devazepide was complemented by indications of improvements in quality-of-life measures. ML's preclinical data indicate that devazepide may similarly enhance the pain-relieving action of milder opiates such as codeine. ML and its development partner Panos Therapeutics expect that a marketing authorization application for the neuropathic pain indication will be submitted in 2003 (1).

1. *Devacade shown to enhance pain relief in phase II clinical trial*. DailyDrugNews.com (Daily Essentials) Sept 3, 2001.

Original monograph - Drugs Fut 1989, 14(9): 862.

Eletriptan



Eletriptan hydrobromide (Relpax™) is a selective 5-$HT_{1B/1D}$ receptor agonist with activity at vascular 5-HT_{1B} receptors and neuronal 5-HT_{1D} receptors, as well as high affinity for 5-HT_{1F} receptors, effective across a range of doses in the acute treatment of migraine with or without aura and its associated symptoms, such as photophobia, phonophobia, vomiting and nausea.

Eletriptan, Pfizer's triptan for the acute treatment of migraine in adults, was approved for market launch via the European mutual recognition procedure in mid-2001. Non-E.U. members, including Norway, also recognized the drug's first E.U. approval in the U.K., where the compound was introduced earlier this year. The antimigraine is also available for prescription in Switzerland and several other countries and the review process is ongoing in the U.S. Ten randomized, double-blind, placebo-controlled studies involving more than 5000 participants in an international clinical program assessed the efficacy, safety and tolerability of the agent. Data indicated that up to 77% of patients treated with the 80-mg dose and 65% of patients treated with the 40-mg dose experienced headache relief at 2 h (1, 2).

Investigators examined the pharmacokinetics of a single oral dose of eletriptan 80 mg taken during each of the 4 cycle phases of the menstrual cycle in 16 healthy volunteers. Eletriptan pharmacokinetics, safety and tolerability did not vary in a clinically significant manner during different phases of the menstrual cycle (3).

Data from a randomized, double-blind, placebo-controlled study were used to determine the cost-effectiveness of oral eletriptan 40 and 80 mg and sumatriptan

50 and 100 mg in acute migraine treatment. Data from 513 patients were analyzed. The cost of successful treatment, defined as pain-free response at 2 h, no recurrence and no use of rescue medication, was lower per patient with eletriptan (4).

Eletriptan 40 and 80 mg was evaluated for the acute treatment of migraine in 1153 patients enrolled in a randomized, double-blind, placebo-controlled, multicenter study. Patients took the assigned medication for 3 attacks. Both doses of eletriptan were effective, well tolerated and demonstrated a rapid onset of action (5). The results of this study and some of those that follow are summarized in Table II.

In a retrospective analysis, data from 7 randomized, double-blind, placebo-controlled trials were utilized to compare tolerability in 253 patients treated with eletriptan plus a selective serotonin reuptake inhibitor (SSRI) with that in 3908 patients who took eletriptan alone. Concomitant administration of eletriptan and an SSRI was well tolerated, with similar rates of adverse events seen in those taking eletriptan alone and those also receiving an SSRI (6).

Researchers evaluated the migraine-specific quality of life of 575 migraine patients enrolled in a randomized, double-blind, placebo-controlled trial comparing eletriptan 40 and 80 mg with ergotamine/caffeine 2 mg/200 mg for the acute treatment of attacks. Eletriptan was superior to ergotamine/caffeine on all 5 domains of the 24-h Migraine Quality of Life Questionnaire (7). Another randomized, double-blind, placebo-controlled trial compared eletriptan (40 and 80 mg) with ergotamine/caffeine tablets (2 tablets of 1 mg/100 mg) in 733 migraine patients. At either dose, significantly more eletriptan-treated patients had a headache response to treatment. Eletriptan was generally well tolerated (8).

Patients (n = 797) treated an acute migraine attack with either placebo, eletriptan 40 or 80 mg or sumatriptan 50 or 100 mg in a double-blind, randomized trial. Eletriptan was significantly superior to placebo and generally superior to sumatriptan according to patient-completed quality-of-life questionnaires (9).

Data from 6 placebo-controlled, comparative trials were reviewed to determine the therapeutic gains over sumatriptan (25, 50 or 100 mg) of eletriptan (20, 40 and 80 mg), naratriptan (1, 2.5 and 5 mg), rizatriptan (5 and 10 mg) and zolmitriptan (5 mg). The clinical efficacy of the triptans studied was highest with eletriptan, followed by rizatriptan, sumatriptan, zolmitriptan and naratriptan (10).

In a meta-analysis of randomized, double-blind studies involving oral triptans it was found that rizatriptan 10 mg and eletriptan 80 mg had higher rates of headache response at 1 h than sumatriptan 100 mg. Efficacy rates at 1 h were higher with subcutaneous sumatriptan than with any of the oral triptans (11).

Investigators analyzed data from 3 randomized, double-blind, placebo-controlled comparative trials to determine the effect of eletriptan (20, 40 and 80 mg) and sumatriptan (50 and 100 mg) on migraine-associated symptoms and functional response in a total of 2282 patients. Patient functionality and acceptability were greater with eletriptan 40 and 80 mg than with either sumatriptan dose. Eletriptan doses of 20, 40 and 80 mg were also superior to placebo in relieving migraine-associated symptoms and in increasing patient acceptability (12).

A multicenter, double-blind, placebo-controlled study compared the efficacy and safety of eletriptan (40 and 80 mg) and zolmitriptan (2.5 mg) for the treatment of a single migraine attack in 1337 patients. The 40-mg dose of eletriptan showed similar response rates to zolmitriptan, whereas the 80-mg dose was consistently better than zolmitriptan. Overall, adverse events with both drugs were mild or moderate, although eletriptan was better tolerated than zolmitriptan (13).

A randomized, placebo-controlled study evaluated eletriptan (40 or 80 mg taken for 1-3 migraine attacks) in migraine patients who had previously responded poorly to oral sumatriptan. Both doses of eletriptan produced 2-h headache response rates superior to placebo and acted rapidly in these patients (14).

A randomized, double-blind, multicenter, placebo-controlled trial evaluated eletriptan 20, 40 and 80 mg in 402 adult Japanese migraine patients. Study medications were taken within 6 h of headache onset. High rates of headache response were seen at 2 h with eletriptan (64, 67 and 76% for the 20, 40 and 80 mg doses, respectively). Eletriptan was well tolerated, with adverse events similar to those observed in Western patients (15).

In a randomized, placebo-controlled, comparative trial in 483 patients with moderate or severe migraine, treatment with oral eletriptan 40 mg showed significantly better response rates and higher treatment acceptability than naratriptan 2.5 mg in the acute treatment of migraine. Headache response rates at 1, 2 and 4 h were 34, 56 and 80%, respectively, for eletriptan compared to 25, 42 and 67%, respectively, for naratriptan. Pain-free response rates at 2 h were 35% for eletriptan and 18% for naratriptan (16).

1. *Relpax approved in E.U. for migraine*. DailyDrugNews.com (Daily Essentials) June 18, 2001.

2. *New migraine therapy available for prescribing in the U.K.* DailyDrugNews.com (Daily Essentials) Feb 12, 2002.

3. Shah, A.K., LaBoy-Goral, L., Scott, N., Morse, T., Apseloff, G. *Pharmacokinetics and safety of oral eletriptan during different phases of the menstrual cycle in healthy volunteers*. J Clin Pharmacol 2001, 41(12): 1339.

4. Wells, N. et al. *A cost-effectiveness analysis of eletriptan 40 mg and 80 mg vs sumatriptan 50 mg and 100 mg in the treatment of migraine attacks*. Cephalalgia 2001, 21(4): Abst P1-F11.

5. Stark, R., Dahlöf, C., Haughie, S., Hettiarachchi, J. *Efficacy, safety and tolerability of oral eletriptan in the acute treatment of migraine: Results of a phase III, multicentre, placebo-controlled study across three attacks*. Cephalalgia 2002, 22(1): 23.

6. Hettiarachchi, J., Turrall, K. *Concomitant eletriptan and selective serotonin reuptake inhibitor therapy for migraine patients: A review of seven clinical studies*. Cephalalgia 2001, 21(4): Abst P2-K60.

Table II: Clinical studies of eletriptan (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Migraine	Randomized, double-blind, multicenter	Eletriptan, 40 mg po sd x 3 attacks Eletriptan, 80 mg po sd x 3 attacks Placebo	1153	Eletriptan was well tolerated and effective in relieving headache in patients with migraine attacks	5
Migraine	Randomized, double-blind, pooled data	Eletriptan (n=3908) Eletriptan + a selective serotonin reuptake inhibitor (n=253)	4161	The combination of eletriptan and a selective serotonin reuptake inhibitor was well tolerated without increasing the incidence of adverse events	6
Migraine	Randomized, double-blind	Eletriptan, 40 mg (n=194) Eletriptan, 80 mg (n=196) Ergotamine tartrate/Caffeine, 2 mg/200 mg (n=185)	575	Eletriptan was more effective in terms of improving migraine-specific quality of life scores compared to ergotamine tartrate/caffeine	7
Migraine	Randomized, double-blind	Eletriptan, 40 mg po sd Eletriptan, 80 mg po sd Ergotamine/Caffeine, 2 mg/200 mg po sd Placebo	733	Eletriptan was well tolerated and more effective than ergotamine/caffeine in relieving pain in patients with migraine attacks	8
Migraine	Randomized, double-blind	Eletriptan, 40 mg (n=163) Eletriptan, 80 mg (n=155) Sumatriptan, 50 mg (n=169) Sumatriptan, 100 mg (n=152) Placebo (n=79)	718	Eletriptan was more effective than sumatriptan in improving migraine-specific quality of life measurements	9
Migraine	Pooled	Eletriptan, 20 mg Eletriptan, 40 mg Eletriptan, 80 mg Sumatriptan, 25 mg Sumatriptan,100 mg Sumatriptan, 50 mg Naratriptan, 1 mg Naratriptan, 2.5 mg Naratriptan, 5 mg Rizatriptan, 5 mg Rizatriptan,10 mg Zolmitriptan, 5 mg		Results from the analysis showed that the order of clinical efficacy of the triptans was eletriptan being the most effective, followed by rizatriptan, sumatriptan, zolmitriptan and naratriptan	10
Migraine	Randomized, double-blind	Eletriptan, 20 mg po Eletriptan, 40 mg po Eletriptan, 80 mg, po Sumatriptan, 100 mg po Naratriptan, 2.5 mg po Zolmitriptan, 2.5 mg po Zolmitriptan, 5 mg po Almotriptan, 12.5 mg po Rizatriptan, 5 mg po Rizatriptan, 10 mg po Placebo		The efficacy data showed that rizatriptan 10 mg and eletriptan 80 mg were better than sumatriptan 100 mg and eletriptan was also superior for 1 h pain-free response. Oral triptans versus sc sumatriptan showed low 1 h efficacy response	11
Migraine	Randomized, double-blind, pooled data	Eletriptan, 20 mg Eletriptan, 40 mg Eletriptan, 80 mg Sumatriptan, 50 mg Sumatriptan, 100 mg	2282	Eletriptan 40 and 80 mg were significantly more effective in improving patient functionality and more acceptable than either sumatriptan dose. Moreover, eletriptan was more effective in relieving photophobia, phonophobia and nausea	12
Migraine	Randomized, double-blind, multicenter	Eletriptan, 40 mg (n=392) Eletriptan, 80 mg (n=396) Zolmitriptan, 2.5 mg (n=405) Placebo (n=144)	1337	Eletriptan 40 and 80 mg was well tolerated with the higher dose being more effective than zolmitriptan 2.5 mg	13
Migraine	Randomized	Eletriptan, 40 mg x 1-3 attacks (n=188) Eletriptan, 80 mg x 1-3 attacks (n=171) Placebo x 1-3 attacks (n=87)	446	Both eletriptan doses were safe, well tolerated and showed very good efficacy in patients with migraine refractory to sumatriptan	14

Continuation

Table II (Cont.): Clinical studies of eletriptan (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Migraine	Randomized, double-blind, multicenter	Eletriptan, 20 mg Eletriptan, 40 mg Eletriptan, 80 mg Placebo	402	All eletriptan doses were well tolerated and produced headache responses superior to placebo in a Japanese population	15
Migraine	Randomized, double-blind, multicenter	Eletriptan, 40 mg (n=192) Naratriptan, 40 mg (n=199) Placebo (n=92)	483	Eletriptan was well tolerated, better accepted and more effective than naratriptan in relieving acute episodes of migraine headache	16

7. Funk Orsini, P.A., Miceli, R.J. *Improvement in migraine-specific quality of life with eletriptan (Relpax™) vs Cafergot®*. Cephalalgia 2001, 21(4): Abst P2-K61.

8. Diener, H.C., Jansen, J.-P., Reches, A., Pascual, J., Pitei, D., Steiner, T.J. *Efficacy, tolerability and safety of oral eletriptan and ergotamine plus caffeine (Cafergot®) in the acute treatment of migraine: A multicentre, randomised, double-blind, placebo-controlled comparison*. Eur Neurol 2002, 47(2): 99.

9. Funk Orsini, P.A., Miceli, R.J. *Comparison of the impact of eletriptan (Relpax™) and sumatriptan on migraine-specific quality of life*. Cephalalgia 2001, 21(4): Abst P2-K62.

10. Mathew, N.T. *Comparison of therapeutic gains over sumatriptan for eletriptan, naratriptan, rizatriptan and zolmitriptan: A review of six clinical studies*. Cephalalgia 2001, 21(4): Abst P2-K6.

11. Roon, K.I., Lipton, R.B., Goadsby, P.J., Ferrari, M.D. *Efficacy of six oral triptans at 1 h post-dose: A meta-analysis*. Cephalalgia 2001, 21(4): Abst P2-K1.

12. Hettiarachchi, J. *Comparison of oral eletriptan and sumatriptan for the improvement of functional disability and the relief of migraine-associated symptoms: A pooled analysis of three randomized clinical studies*. Neurology 2001, 56(8, Suppl. 3): Abst S42.005.

13. Diener, H.-C., MacGregor, A.E., Shoenen, J., Steiner, T.J., Muirhead, N., Sikes, C. *Comparison of the efficacy and safety of eletriptan and zolmitriptan for the acute treatment of migraine: Results of a multicenter, multi-dose, randomized clinical trial*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P04.081.

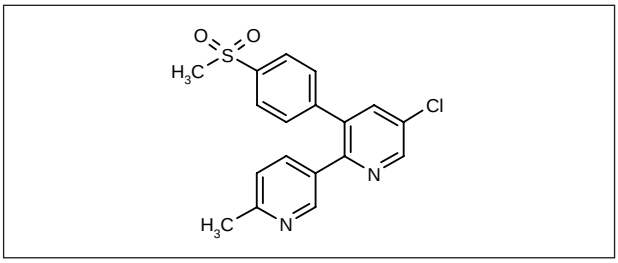
14. Farkkila, M. et al. *Eletriptan for the treatment of migraine in poor responders to oral sumatriptan: A randomized, placebo-controlled study*. Cephalalgia 2001, 21(4): Abst PL-8.

15. Fukuuchi, Y., Sakai, F. *Efficacy and safety of eleptriptan 20 mg, 40 mg and 80 mg in Japanese migraineurs*. Cephalalgia 2001, 21(4): Abst LB-9.

16. Garcia-Ramos, G., MacGregor, A.E. *Comparison of the efficacy and safety of eletriptan and naratriptan for the treatment of a single migraine attack: Results of a multicenter, randomized, placebo-controlled trial*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P04.077.

Original monograph - Drugs Fut 1997, 22(3): 221.

Etoricoxib



The COX-2-selective inhibitor etoricoxib (L-791456, MK-0663, MK-663) has just been introduced by Merck, Sharp & Dohme (Merck & Co.) in the U.K. as Arcoxia™. The U.K. was the first country of the European Union to grant marketing approval for etoricoxib.

Etorixocib is indicated for the once-daily symptomatic relief of osteoarthritis and rheumatoid arthritis, the treatment of acute gouty arthritis, the relief of chronic musculoskeletal pain, including chronic low back pain, the relief of acute pain associated with dental surgery and the treatment of primary dysmenorrhea. Available as tablets of 60, 90 and 120 mg, it has also been approved in Peru, Mexico and Brazil. Merck recently withdrew its original NDA in the U.S. and intends to submit an expanded NDA to the FDA with new efficacy data to support an indication for ankylosing spondylitis, in addition to the above indications (1-4).

In vitro metabolism studies were conducted to identify etoricoxib metabolites and their effects on COX-1 and COX-2 activities. The metabolites did not demonstrate potent COX-1 or COX-2 inhibition and are not expected to alter the selectivity profile of etoricoxib. Etoricoxib did not show major metabolic liabilities in humans (5).

The preclinical profile of etoricoxib and comparison with other selective COX-2 inhibitors indicate potential therapeutic advantages for this compound in the treatment of osteoarthritis and other inflammatory conditions. Etoricoxib displays high potency against COX-2 and high selectivity relative to COX-1 in human whole blood assays (IC_{50} = 1.1 and 116 μM, respectively), as well as in CHO cells expressing recombinant human COX-2 and COX-1 (IC_{50} = 79 and 50 μM, respectively). The COX-2 selectivity of etoricoxib (selectivity ratio of 106 in whole blood) was much greater than that of rofecoxib (35), valdecoxib (30), celecoxib (7.6) and nimesulide (7.3), other purportedly COX-2-selective agents. Also, assays

designed to compare the potential for COX-1 inhibition at low arachidonic acid levels demonstrated the same rank order of potency for these compounds and significantly reduced potency for etoricoxib compared to the other COX-2-selective agents. Potent activity was seen in the carrageenan-induced paw edema, carrageenan-induced paw hyperalgesia, lipopolysaccharide-induced pyresis and adjuvant-induced arthritis models in rats, with respective ID_{50} values for etoricoxib of 0.64, 0.34, 0.88 and 0.6 mg/kg/day orally. It was also effective in reversing endotoxin-induced pyresis in squirrel monkeys (81% inhibition at 3 mg/kg p.o.). The *in vivo* efficacy of etoricoxib in these tests was generally comparable to rofecoxib and indomethacin. The gastrointestinal tolerability of etoricoxib, as evaluated in models of urinary ^{51}Cr excretion in rats and of fecal ^{51}Cr excretion in squirrel monkeys, was excellent, the compound having no effects at respective doses of 200 mg/kg/day for up to 10 days and 100 mg/kg/day for up to 5 days, whereas much lower doses of diclofenac (1-3 mg/kg/day), naproxen (10 mg/kg/day) or indomethacin (3 mg/kg/day) significantly increased chromium excretion in these assays (6).

To investigate the single-dose pharmacokinetics of etoricoxib, 12 healthy subjects were given single oral doses of 120 mg in the fasted and fed state and a single i.v. dose of 25 mg in a crossover manner, while 12 were given 30, 60, 120 and 240 mg as single oral doses. Multiple-dose pharmacokinetics of the drug were determined in 24 healthy subjects given 120 mg daily. Etoricoxib demonstrated linear kinetics, and rapid and high absorption. Absorption was not affected by food intake (7).

A randomized, crossover study investigated the pharmacokinetics of [^{14}C]-etoricoxib in 6 healthy volunteers. The agent was administered as a single i.v. dose of 25 mg and as a single dose of 100 mg as oral solution. A high degree of absorption was observed, along with substantial oxidative biotransformation. The excretion of the 5 metabolites identified was primarily renal (8).

Researchers found that the pharmacokinetics of etoricoxib were linear when the drug was administered to 12 healthy volunteers as single oral doses of 5, 10, 20, 40 and 120 mg. All doses were well tolerated (9).

Etoricoxib is expected to be associated with reduced gastrointestinal microbleeding compared to conventional NSAIDs. In a 28-day double-blind trial in 62 healthy volunteers, doses twice those with maximal efficacy in osteoarthritis (120 mg once daily) had equivalent effects to placebo on mean daily fecal blood loss, whereas therapeutic doses of ibuprofen (800 mg t.i.d.) significantly increased fecal blood loss (10, 11).

In a double-blind, randomized, crossover trial in healthy volunteers to test the hypothesis that etoricoxib spares PGE_2 synthesis in human gastric mucosa, 29 volunteers received etoricoxib 120 mg/day or placebo for 5 days, and another 10 volunteers received naproxen 500 mg b.i.d. or placebo. Although these doses of etoricoxib (75%) and naproxen (69%) showed equivalent inhibition of COX-2, measured as inhibition of lipopolysaccharide-stimulated PGE_2 synthesis in whole blood, unlike naproxen (78% inhibition), etoricoxib (2% inhibition) was not associated with significant inhibition of gastric mucosal PGE_2 synthesis compared to placebo (12).

Data from the active comparator-controlled treatment periods of 8 randomized, double-blind phase II/III trials of etoricoxib in patients with osteoarthritis, rheumatoid arthritis and chronic low back pain have been reported. The trials involved 2651 patients who were treated with once-daily etoricoxib and 1329 patients treated with diclofenac or naproxen. The results showed a significant 43% reduction in treatment discontinuations due to nonselective NSAID-type gastrointestinal symptoms, as well as discontinuations due to gastrointestinal symptoms in general, on etoricoxib compared to the nonselective NSAIDs. Treatment with etoricoxib was also associated with a significantly reduced need for gastroprotective agents and gastrointestinal comedications in general of approximately 45% compared to the nonselective NSAIDs (13, 14). Analysis of data from over 3000 patients treated with once-daily etoricoxib and 1799 treated with the nonselective NSAIDs diclofenac, ibuprofen or naproxen demonstrated a significant reduction in the incidence of investigator-reported and confirmed upper gastrointestinal perforations, ulcers and bleeds of about 50% in the etoricoxib-treated patients (15).

According to clinical trial results in patients with osteoarthritis, the efficacy of etoricoxib is paralleled by improvements in quality of life. Data from 2 multicenter, double-blind, randomized phase III trials in 997 patients with osteoarthritis of the knee or hip experiencing flare upon discontinuation of therapy were analyzed. The patients were randomized to etoricoxib 60 mg once daily, naproxen 500 mg twice daily or placebo for 12 weeks. In terms of primary efficacy measures (WOMAC pain and physical function subscales and patient global assessment of disease status), etoricoxib and naproxen were similarly active and superior to placebo, and well tolerated. Compared to placebo, etoricoxib was associated with significantly greater improvement in 7 of 8 SF-36 domains, as well as on the Physical and Mental Component Summary scores. No significant differences were seen between etoricoxib and naproxen (16).

In a randomized, double-blind, placebo-controlled study, 200 patients with moderate to severe pain after removal of at least 2 third molars were given single doses of etoricoxib 120 mg, naproxen sodium 550 mg, acetaminophen/codeine 600/60 mg or placebo. Etoricoxib and naproxen provided similar analgesia, which was significantly superior to acetaminophen/codeine (17) (Table III).

In a multicenter, double-blind, randomized, placebo-controlled trial, 617 patients with osteoarthritis of the knee and increased pain upon NSAID withdrawal were randomized to receive once-daily etoricoxib at doses of 5, 10, 30, 60 or 90 mg or placebo for 6 weeks, followed by continuation or reallocation to etoricoxib 30, 60 or 90 mg or diclofenac 150 mg for a total of 52 weeks. Significantly greater efficacy for etoricoxib compared to placebo was demonstrated in the first part, which was

Table III: Clinical studies of etoricoxib (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Pain	Randomized, double-blind	Etoricoxib, 120 mg sd po (n=50) Naproxen, 550 mg sd po (n=50) Acetaminophen/codeine, 600/60 mg sd po (n=50) Placebo (n=50)	200	Etoricoxib was well tolerated and equally effective as naproxen and significantly greater than paracetamol/ codeine in relieving acute dental pain	17
Back pain	Randomized	Etoricoxib, 60 mg po od x 12 wk (n=103) Etoricoxib, 90 mg po od x 12 wk (n=107) Placebo (n=109)	319	Etoricoxib was well tolerated and effective in improving disability scores and producing pain relief in patients with chronic low back pain	19

strongly dose-dependent. In the second part of the study, efficacy was generally maintained and the two higher doses were more effective than the 30-mg dose of etoricoxib. Etoricoxib was reported to be well tolerated in general over the entire study period, with no significant dose-related trend for adverse events (18).

Etoricoxib was evaluated over 3 months in a trial in 319 patients with chronic low back pain. The subjects were randomized to receive etoricoxib as once-daily doses of 60 or 90 mg or placebo. The results showed that both doses of etoricoxib provided significant pain relief and improvement in disability at 4 weeks, with significant differences compared to placebo seen already at 2 weeks. The effects of etoricoxib were also sustained over the entire study and it was generally well tolerated (19) (Table III).

1. *Recent launch of new COX-2 inhibitor for acute and chronic painful conditions*. DailyDrugNews.com (Daily Essentials) May 15, 2002.

2. *Arcoxia granted major approval for relief of arthritis and pain*. DailyDrugNews.com (Daily Essentials) April 17, 2002.

3. *Merck & Co. to submit expanded NDA for Arcoxia*. DailyDrugNews.com (Daily Essentials) March 18, 2002.

4. *Biochemical studies with etoricoxib in man consistent with GI-sparing antiinflammatory profile*. DailyDrugNews.com (Daily Essentials) Oct 16, 2001.

5. Chauret, N., Yergey, J.A., Brideau, C., Friesen, R.W., Mancini, J., Riendeau, D., Silva, J., Styhler, A., Trimble, L.A., Nicoll-Griffith, D.A. *In vitro metabolism considerations, including activity testing of metabolites, in the discovery and selection of the COX-2 inhibitor etoricoxib (MK-0663)*. Bioorg Med Chem Lett 2001, 11(8): 1059.

6. Riendeau, D., Percival, M.D., Brideau, C. et al. *Etoricoxib (MK-0663): Preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2*. J Pharmacol Exp Ther 2001, 296(2): 558.

7. Agrawal, N.G., Matthews, C.Z., Rose, M.J. et al. *Single- and multiple-dose pharmacokinetics of etoricoxib, a highly selective inhibitor of cyclooxygenase-2, in healthy subjects*. Clin Pharmacol Ther 2002, 71(2): Abst TPII-34.

8. Agrawal, N.G., Geer, L.A., Cui, D. et al. *Disposition of [^{14}C] etoricoxib in healthy subjects*. Clin Pharmacol Ther 2002, 71(2): Abst TPII32.

9. Agrawal, N.G.B., Porras, A.G., Matthews, C.Z., Woolf, E.J., Miller, J.L., Mukhopadhyay, S., Neu, D.C., Gottesdiener, K.M. *Dose proportionality of oral etoricoxib, a highly selective cyclooxygenase-2 inhibitor, in healthy volunteers*. J Clin Pharmacol 2001, 41(10): 1106.

10. Hunt, R.H., Bowen, H., James, C., Marshall, J., Simon, T., Callegari, P., Cagliola, A., Yu, C., Lines, C. *COX-2 specific inhibition with MK-0663 120 mg q.d. over 4 weeks did not increase fecal blood loss: A controlled study with placebo and ibuprofen 800 mg t.i.d.* Dig Dis Week (May 20-23, Atlanta) 2001, Abst 3031.

11. Hunt, R.H., Callegari, P., Bowen, B., James, C., Marhall, J., Montensen, E., Cagliola, A., Yu, C., Quan, H., Simon, T. *COX-2 specific inhibition with MK-0663 120 mg q.d. over 4 weeks did not increase fecal blood loss: A controlled study with placebo and ibuprofen 800 mg t.i.d.* Annu Eur Congr Rheumatol (June 13-16, Prague) 2001, Abst SAT0051.

12. Wight, N.J., Gottesdiener, K., Wong, P., Calder, N., Cote, J., Hawkey, C.J. *Sparing of gastric mucosal prostaglandin synthesis in humans by etoricoxib, a new COX-2 selective inhibitor*. Gut 2001, 49(Suppl. 3): Abst 2865.

13. Harper, S.E., Bolognese, J., Lee, M., Watson, D., Curtis, S. *Fewer GI-related treatment discontinuations with etoricoxib compared with non-selective nonsteroidal antiinflammatory drugs*. J Gastroenterol Hepatol 2002, 17(Suppl.): Abst P.C.039.

14. Harper, S.E., Bolognese, J., Lee, M., Watson, D., Curtis, S. *Treatment with etoricoxib required fewer concomitant gastroprotective agents than non-selective nonsteroidal antiinflammatory drugs*. J Gastroenterol Hepatol 2002, 17(Suppl.): Abst P.C.040.

15. Harper, S., Lee, M., Curtis, S., Ng, J., Watson, D., Bolognese, J. *A lower incidence of upper-GI perforations, ulcers and bleeds in patients treated with etoricoxib vs. non-selective nonsteroidal antiinflammatory drugs*. J Gastroenterol Hepatol 2002, 17(Suppl.): Abst P.C.041.

16. Curtis, S.P., Leung, A., Watson, D.J., Ramey, D., Kong, S., Harper, S. *Improved quality-of-life (QoL) with etoricoxib compared with placebo in patients with osteoarthritis*. Osteoarthritis Cartilage 2001, 9(Suppl. B): Abst PA18.

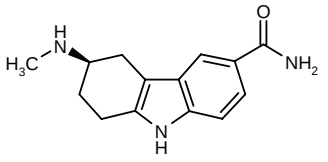
17. Malmstrom, K., Kotey, P., Coughlin, H., Daniels, S., Desjardins, P.J. *Efficacy of etoricoxib, naproxen sodium, and acetaminophen/codeine in acute dental pain*. Clin Pharmacol Ther 2001, 69(2): Abst PI-6.

18. Curtis, S.P., Fisher, C., Kafka, S. et al. *Treatment with etoricoxib (MK-0663), a COX-2 selective inhibitor, resulted in clinical improvement in knee osteoarthritis (OA) over 52 weeks*. Annu Eur Congr Rheumatol (June 13-16, Prague) 2001, Abst SAT0064.

19. Geba, G.P., Puopolo, A.D., Birbara, C., Jackson, R.E., Bohidar, N.R., O'Brien, K., Skalky, C.S. *Treatment of chronic low back pain (LBP) with etoricoxib, a new cyclo-oxygenase-2 selective inhibitor: A three-month placebo-controlled trial*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 647.

Original monograph - Drugs Fut 2001, 26(4): 346.

Frovatriptan



Frovatriptan (VML-251), a 5-$HT_{1B/1D}$ receptor agonist developed by Vernalis, has been approved in the U.S. and the E U. for the acute treatment of migraine.

Approval of frovatriptan follows studies that showed that a single 2.5-mg dose of the drug was effective for the treatment of migraine attacks, has a prolonged presence in the bloodstream and that few patients experienced a recurrence within a 24-h period. Elan, Vernalis's marketing partner in the U.S., plans to market the drug under the name Frova™, where it will be copromoted with UCB. In Europe, frovatriptan was first approved in France (Migard®), followed by successful completion of the mutual recognition procedure in the other E.U. countries. Vernalis has partnered with Menarini for European marketing, with the first launch expected in the first half of 2002. The company is also continuing clinical trials in order to expand approved labeling (1-6).

Enrollment has been initiated in a 400-patient multicenter study with frovatriptan in the U.S. for the prevention of menstrually associated migraine attacks (7).

The therapeutic index of frovatriptan was evaluated in a review of adverse events from 21 studies involving 369 subjects. Adverse events that occurred within 48 h of the final dose from each treatment period were analyzed in relation to frovatriptan exposure, as indicated by C_{max} values. Although the incidence of adverse events was higher in the frovatriptan periods than in the placebo periods, the drug was found to have a broad therapeutic index. Only when frovatriptan C_{max} values were > 50 ng/ml, corresponding to mean blood levels achieved at 6-10 times the clinical dose of 2.5 mg, did adverse events increase (8).

A randomized, double-blind, multicenter, placebo-controlled trial was conducted in 635 migraine patients to determine the optimal dose of frovatriptan for acute migraine treatment. Patients took single oral doses of placebo or frovatriptan 0.5, 1, 2.5 or 5 mg at headache onset. Optimal efficacy and tolerability were observed with the 2.5-mg dose (9). Results of this and the following 2 studies are summarized in Table IV.

The effect of CYP1A2 inhibitors on the metabolic clearance of frovatriptan was evaluated in a crossover study including 24 subjects: 8 men and 8 women using the combined oral contraceptive (COC) pill, which inhibits CYP1A2, and 8 female non-COC users. Oral frovatriptan 2.5 mg was administered alone or on day 8 of an 11-day treatment with fluvoxamine 100 mg daily. Administration of 100 mg caffeine and measurement of the urinary caffeine metabolite ratio confirmed that fluvoxamine strongly inhibited CYP1A2. The systemic exposure to coadministered frovatriptan was increased, with the frovatriptan $AUC_{0\text{-}24h}$ increased by 39, 41 and 28% in male COC users, female COC users and female non-COC users, respectively. C_{max} was increased by 28, 49 and 27% in these groups, respectively. The mean $t_{1/2}$ of frovatriptan was similar in all groups and was shorter when coadministered with fluvoxamine than when taken alone (17 h *vs*.

Table IV: Clinical studies of frovatriptan (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Migraine	Randomized, double-blind, multicenter	Frovatriptan, 0.5 mg po sd if moderate to severe attack (n=133) Frovatriptan, 1 mg po sd if moderate to severe attack (n=122) Frovatriptan, 2.5 mg po sd if moderate to severe attack (n=131) Frovatriptan, 5 mg po sd if moderate to severe attack (n=126) Placebo (n=123)	635	Frovatriptan 2.5 mg appeared to offer an optimal efficacy and tolerability for the treatment of migraine attacks	9
Healthy Volunteers	Open, crossover	Frovatriptan, 2.5 mg po od x 19 Frovatriptan, 2.5 mg po od x 18 d → (after 17 days) Fluvoxamine, 100 mg/d po od x 11 d	24	Frovatriptan was well tolerated and could be coadministered with fluvoxamine without dose adjustments in healthy women	10
Migraine	Open	Frovatriptan, 2.5 mg po if migraine attack over 6 mo Frovatriptan, 2.5 mg po if migraine attack over 1 y		Frovatriptan produced sustained headache relief irrespective of initial severity	11

24 h). Female COC users had the highest frovatriptan exposure due to the inhibition of CYP1A2 by both fluvoxamine and COC. Men had the lowest frovatriptan exposure. The difference in AUC_{0-24h} between genders was 10-30%. C_{max} values were highest for female COC users but were similar in men and women not using COC. C_{max} values of frovatriptan were well below those found in other studies where frovatriptan 40 mg was well tolerated. It was concluded that coadministration with fluvoxamine or any other potent CYP1A2 inhibitor is safe and does not warrant dose adjustment (10).

Open-label studies of 6 and 12 months of frovatriptan 2.5 mg have shown that the drug might be useful in the treatment of mild migraine headache. In each study, patients recorded the time to meaningful relief, defined as resolution of headache pain and other migraine symptoms. In both studies, the median time to relief was related to the initial severity of the headache, with headaches of greater initial severity taking longer to resolve. The incidence of recurrence was low and was not related to headache severity (11).

1. *Elan appoints UCB as U.S. copromotion partner for Frova.* DailyDrugNews.com (Daily Essentials) April 2, 2002.

2. *FDA approves frovatriptan for treatment of migraine*. DailyDrugNews.com (Daily Essentials) Nov 14, 2001.

3. *Frovatriptan completes mutual recognition procedure for E.U.-wide approval*. DailyDrugNews.com (Daily Essentials) Jan 25, 2002.

4. *Vernalis makes significant progress during past year*. DailyDrugNews.com (Daily Essentials) April 4, 2001.

5. *Elan: 2001 review, 2002 projections*. DailyDrugNews.com (Daily Essentials) Feb 8, 2002.

6. *Vernalis expands frovatriptan collaboration with Elan; company to buy out royalties from SB*. DailyDrugNews.com (Daily Essentials) Dec 29, 2000.

7. *Vernalis presents annual progress review*. DailyDrugNews.com (Daily Essentials) March 25, 2002.

8. Keywood, C., Wetherill, G., Sugden, P. *Frovatriptan broad therapeutic index: Relationship of adverse events occurrence to frovatriptan blood levels*. Cephalalgia 2001, 21(4): Abst P1-H23.

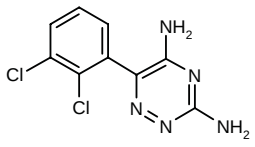
9. Goldstein, J., Keywood, C. *Frovatriptan for the acute treatment of migraine: A dose-finding study*. Headache 2002, 42(1): 41.

10. Wade, A., Buchan, P., Mani, T., Ward, C. *Frovatriptan has no clinically significant interaction with fluvoxamine*. Cephalalgia 2001, 21(4): Abst P2-K49.

11. Cady, R., Keywood, C. *Frovatriptan: Preliminary efficacy in the early treatment of migraine attacks*. Cephalalgia 2001, 21(4): Abst P2-K48.

Original monograph - Drugs Fut 1997, 22(7): 725.

Lamotrigine



Lamotrigine (GlaxoSmithKline's Lamictal®) is a new-generation antiepileptic agent with proven efficacy as add-on therapy and monotherapy in patients with epilepsy. The compound acts via use-dependent inhibition of voltage-dependent neuronal sodium channels, a mechanism also postulated to be useful in the treatment of chronic pain.

Two new syntheses of lamotrigine have been reported:

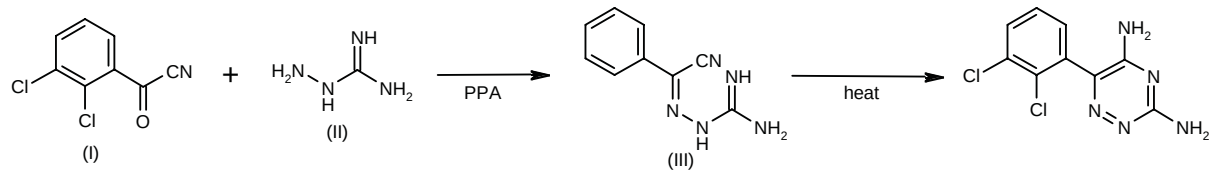
Condensation of 2,3-dichlorobenzoyl cyanide (I) with aminoguanidine (II) by means of PPA in hot acetonitrile yields 2,3-dichlorobenzoyl cyanide amidinohydrazone (III), which is cyclized to the target 1,2,4-triazine by heating in refluxing propanol with or without DMSO (1). Scheme 1.

Hydrogenation of 2,3-dichloronitrobenzene (I) with H_2 over Ra-Ni in methanol gives 2,3-dichloroaniline (II), which is diazotized with $NaNO_2$ and HCl and treated with CuCN to yield 2,3-dichlorobenzonitrile (III). Hydrolysis of the nitrile (III) with NaOH in refluxing methanol/water affords 2,3-dichlorobenzoic acid (IV), which is treated with hot $SOCl_2$ to provide the corresponding acyl chloride (V). Reaction of (V) with CuCN and KI in refluxing chlorobenzene gives 2,3-dichlorobenzoyl cyanide (VI), which is condensed with aminoguanidine (VII) by means of H_2SO_4/TsOH in hot toluene to yield 2,3-dichlorobenzoyl cyanide amidinohydrazone (VIII). Finally, this compound is cyclized by treatment with NaOMe in refluxing methanol (2). Scheme 2.

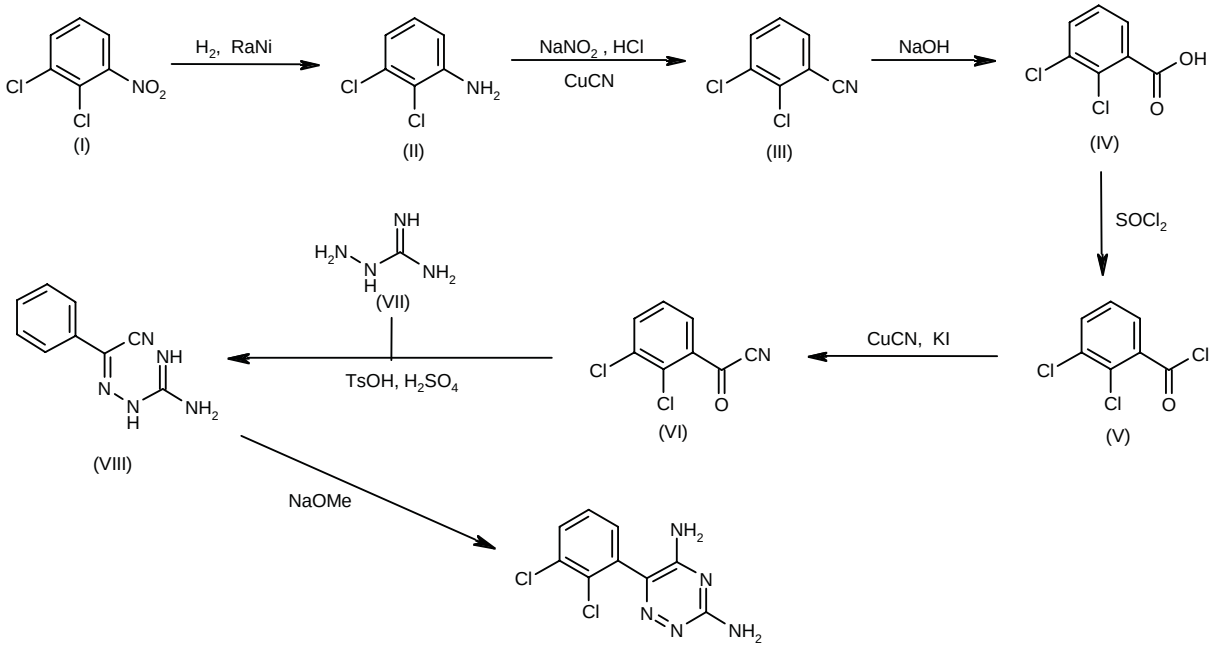
Results from preclinical models and early clinical studies indicating a role for lamotrigine in the treatment of neuropathic pain led a researcher at Craigavon Area Hospital to review the literature and evaluate the accumulating evidence for this potential new use for lamotrigine. Lamotrigine has demonstrated efficacy in rodent models of mechanical hyperalgesia and cold allodynia, while having no effect on acute pain reflexes. Moreover, clinical efficacy has been reported in patients with trigeminal neuralgia, painful HIV-associated peripheral neuropathy, diabetic neuropathy, neuropathic pain associated with multiple sclerosis and several other neuropathic pain states. The author concludes that further large, randomized trials should be conducted to confirm these promising preliminary results (3).

The antinociceptive effects of gabapentin and lamotrigine were assessed in a rat model of trigeminal neuropathic pain in which acute and repeat injections of the drugs were administered to rats with chronic constriction of one infraorbital nerve. Only repeated injections of gabapentin 30 and 50 mg/kg partially alleviated

Scheme 1: Synthesis of Lamotrigine



Scheme 2: Synthesis of Lamotrigine



hyperresponsiveness, suggesting the superiority of gabapentin over lamotrigine for this disorder (4).

A total of 227 patients with painful HIV-associated distal sensory polyneuropathy were enrolled in a multicenter, randomized, double-blind, placebo-controlled clinical study of lamotrigine. Patients in 2 groups, those on and those not on neurotoxic dideoxynucleoside antiretroviral therapy (ART), were randomized to treatment with placebo or lamotrigine titrated up over 7 weeks and maintained at 400-600 mg/day for 4 weeks. Lamotrigine was safe and improved neuropathic pain in these patients. Pain relief was equivalent for those taking lamotrigine and placebo in the group not taking neurotoxic ART (5). The results of this study and some of those that follow are summarized in Table V.

Investigators randomized 59 patients with pain associated with diabetic neuropathy to lamotrigine (titrated from 25 to 400 mg/day) or placebo in a 6-week study. Adverse events were similar in both groups, and lamotrigine reduced numerical pain scale scores to a greater extent than placebo (6).

An open-label study evaluated the use of lamotrigine (titrated at 25 mg/week, 280 mg/day mean dose) as add-on medication for chronic refractory neuropathic pain in 35 patients. Treatment for 4 months or longer led to reductions in pain scores in 14 patients and was well tolerated (7). In another recent study, 35 refractory chronic pain patients received an average dose of 260 mg/day of lamotrigine as add-on medication. Lamotrigine proved effective and safe for the treatment of refractory neuropathic pain syndromes (8).

Lamotrigine 125-200 mg was administered to 5 patients with short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing,

Table V: Clinical studies of lamotrigine (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
HIV infection, peripheral neuropathy, polyneuropathy	Randomized, double-blind, multicenter	Lamotrigine, 400-600 mg/d (titrated over 7 wk) x 4 wk maintenance Placebo	227	Lamotrigine was well tolerated and effective in improving neuropathic pain in HIV peripheral neuropathy independently of the dideoxynucleoside antiretroviral drug intake	5
Diabetic neuropathy	Randomized double-blind	Lamotrigine, 25 mg od x 2 wk → 25-400 mg/d bid (up to 50, 100, 150, 200 or 400 mg bid each dose for an additional wk) x 6 wk (n=29) Placebo (n=30)	59	Lamotrigine was safe but did not show changes on mood and pain scales, probably due to the short period of treatment at an effective dose	6
Diabetic neuropathy, neuroma	Open, multicenter	Lamotrigine, 25 mg/wk (mean of 280 mg/d, titrated every wk if needed) x 4 mo (mean)	35	Preliminary results suggest that lamotrigine was safe and well tolerated, and could be effective in relieving pain in patients with refractory neuropathic pain syndromes	7
Peripheral neuropathy	Open	Lamotrigine, 25 mg/wk → 260 (mean) mg/d (titrated every week if needed) x 4 mo	35	Lamotrigine could be effective in the treatment of neuropathic pain syndromes	8
Cerebro-vascular accident	Double-blind, crossover, multicenter, retrospective	Lamotrigine, 200 mg/d po x 8 wk (titrated every 2 wk from 25 mg/d) Placebo	30	Lamotrigine 200 mg was well tolerated and moderately effective in central poststroke pain, and might be an alternative to amitriptyline	11
Polyneuropathy	Randomized, double-blind	Lamotrigine, 200-500 mg/d (titrated until response) Placebo	21	Lamotrigine was safe and effective in painful polyneuropathy	13

a rare condition considered to be intractable. Complete remission was achieved in 3 patients and attack frequency was reduced by approximately 80% in 2 patients (9).

Data from randomized, double-blind, placebo-controlled trials of analgesics in postherpetic neuralgia and painful diabetic neuropathy were collected to assess the true effect size of the drugs on pain parameters. The true effect sizes (expressed as response on drug minus response on placebo) for various agents in terms of ongoing pain intensity were amitriptyline 11-25%, desipramine 8-33%, gabapentin 18-26%, lamotrigine 16%, tramadol 26-28% and oxycodone 32% (10).

Patients with central poststroke pain (n=30) took part in a multicenter, randomized, double-blind, placebo-controlled, crossover study of treatment with lamotrigine. Lamotrigine was titrated every second week from 25 to 50 to 100 mg/day, ending at 200 mg/day. Treatment was for two 8-week periods with 2 weeks of washout in between. Lamotrigine 200 mg/day reduced pain in these patients and was well tolerated (11).

A 2-week treatment with lamotrigine (50 mg/day for 1 week followed by 100 mg/day for 1 week) resolved the persistent visual phenomena experienced by 2 female migraine patients for 3 months and 3 years, respectively (12).

In a randomized, double-blind, placebo-controlled study, 21 patients with painful polyneuropathy received lamotrigine (titrated to 200 mg/day, maximum 500 mg/day) or placebo. Patients given lamotrigine tolerated the drug well and achieved significantly lower mean pain scores than those given placebo (13).

Lamotrigine 25-200 mg/day was evaluated in 65 patients with migraine or chronic daily headache in an open-label study. The treatment was effective in reducing headache frequency, especially when aura was present. Lamotrigine efficacy was reduced in patients with analgesic overuse (14).

1. Nadaka, V. et al. (Chemagis Ltd.). *Process for preparing substd. benzoyl cyanide amidinohydrazones*. EP 1127873.

2. Radhakrishnan, T.V. et al. (RPG Life Sciences Ltd.). *A process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, commonly known as lamotrigine*. WO 0149669.

3. McCleane, G.J. *Lamotrigine in the management of neuropathic pain: A review of the literature*. Clin J Pain 2000, 16(4): 321.

4. Christensen, D., Gautron, M., Guilbaud, G., Kayser, V. *Effect of gabapentin and lamotrigine on mechanical allodynia-like behaviour in a rat model of trigeminal neuropathic pain*. Pain 2001, 93(2): 147.

5. Simpson, D.M., McArthur, J.C., Olney, R., Ross, D., Barrett, P., Baird, B.J. *A multicenter, double-blind, randomized, placebo-controlled evaluation of lamotrigine in adult subjects with painful HIV-associated peripheral neuropathy*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst S52.007.

6. Eisenberg, E., Lurie, Y., Braker, C., Daoud, C., Ishay, A. *Lamotrigine reduces painful diabetic neuropathy – A randomized, controlled study*. Neurology 2001, 57(3): 505.

7. Longmire, D.R., Russellville, J.C.K. *Lamotrigine in the treatment of chronic refractory neuropathic pain*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P06.121.

8. Krusz, J.C. *Lamotrigine in the treatment of neuropathic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 758.

9. D'Andrea, G., Granella, F., Ghiotto, N., Nappi, G. *Lamotrigine in the treatment of SUNCT syndrome*. Neurology 2001, 57(9): 1723.

10. Babul, N., Watson, C.P.N. *Effect size of commonly used pharmacologic agents in neuropathic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 664.

11. Vestergaard, K., Andersen, G., Gottrup, H., Kristensen, B.T., Jensen, T.S. *Lamotrigine for central poststroke pain. A randomized controlled trial*. Neurology 2001, 56(2): 184.

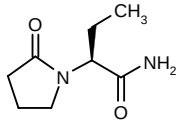
12. Chen, W.T., Fuh, J.-L., Lu, S.-R., Wang, S.-J. *Persistent migrainous visual phenomena might be responsive to lamotrigine*. Headache 2001, 41(8): 823.

13. Hart, D.E., Riback, P.S., Calder, C.S., Storey, J.R., Wymer, J.P., Potter, D.L. *Lamotrigine for painful polyneuropathy: Randomized, placebo-controlled, double-blind, parallel-group pilot study*. 126th Annu Meet Am Neurol Assoc (Sept 30-Oct 3, Chicago) 2001, 49.

14. Wheeler, S.D. et al. *Lamotrigine efficacy in migraine prevention*. Cephalalgia 2001, 21(4): Abst P2-I14.

Original monograph - Drugs Fut 1986, 11(6): 456.

Levetiracetam



Levetiracetam (Keppra®), developed by UCB, was approved in the U.S. in 1999 as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. It is also approved in several European countries. Lundbeck holds marketing rights to the drug in Canada, where it is under review by the regulatory authorities (1). The drug is also under evaluation for the treatment of neuropathic pain and migraine.

Levetiracetam treatment was tested in 11 patients with chronic pain to see if the drug could improve neuropathic pain symptoms. Levetiracetam 250 mg was given for 5 days and increased by 250 mg to approximately 2000 mg/day in two divided doses. Reductions in pain scores and intensity indicated that the drug was effective in this population and merits further study for this indication (2).

Patients (n = 38) with refractory chronic neuropathic pain received progressively higher doses of levetiracetam (1500-6500 mg/day). The drug induced an average 69.4% decrease in the pain scores in 10 patients and another 10 patients reported pain reductions of < 50%, thus confirming the initial findings of efficacy and safety in the treatment of chronic neuropathic pain (3). The results of this and the following studies are summarized in Table VI.

A study was performed in 62 patients with refractory migraine, treated initially with 500 mg b.i.d. levetiracetam, increasing up to 1500 mg b.i.d. as required. Levetiracetam significantly reduced headache frequency and severity at the highest dose after the first month. Although side effects were infrequent at lower doses, they increased at the higher effective doses. Ten patients discontinued therapy due to lack of efficacy or side effects, which included drowsiness, nausea and increased headache. Overall, investigators considered that further evaluation of levetiracetam in the treatment of headache and pain is warranted (4).

A recent study evaluated the addition of 500 mg/day of levetiracetam to treatment with the anticonvulsant gabapentin (300-2400 mg) in 10 patients with neuropathic pain. A total of 60% of the patients reported at least a 50% reduction in pain symptoms following the addition of levetiracetam, suggesting its use in combination therapies for neuropathic pain (5).

Levetiracetam has been assessed for its use in the prophylaxis of migraine in two separate studies. An open-label trial was conducted in 30 patients failing or responding poorly to treatment with other neuronal stabilizing agents, all of whom had an average of at least 2 migraine episodes per week. Levetiracetam was started at 250 mg in the evening, with increases over 1 month to 1000 mg twice daily and further dose adjustments during the trial. A reduction of over 50% in migraine frequency and severity was reported by 14 patients after 3 months of treatment and 12 patients could discontinue or reduce the dose of prior antimigraine medications. A dose of up to 4500 mg/day was required in some cases. Four other patients had 25-50% improvement, 4 were not yet evaluable, and 8 patients showed no response or discontinued due to adverse events (6).

1. *Lundbeck gains exclusive marketing rights to Keppra in Canada*. DailyDrugNews.com (Daily Essentials) Jan 14, 2002.

2. Krusz, J.C. *Levetiracetam (Keppra): Novel agent for refractory chronic neuropathic pain*. 17th World Congr Neurol (June 17-22, London) 2001, Abst P1363.

3. Krusz, J.C. *Levetiracetam for chronic neuropathic pain treatment*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 759.

4. Drake, M.E., Greathouse, N.I., Armentbright, A.D., Benner, J.B. *Levetiracetam for preventive treatment of migraine*. Cephalalgia 2001, 21(4): Abst P2-I13.

5. Bhakta, B., Ward, S., Jenson, M., Royal, M., Movva, V., Gunyea, I. *Gabapentin and levetiracetam in combination for the treatment of neuropathic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 750.

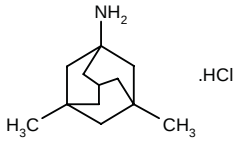
6. Krusz, J.C. *Levetiracetam as prophylaxis for resistant headaches*. Cephalalgia 2001, 21(4): Abst P2-I12.

Original monograph - Drugs Fut 1994, 19(2): 111.

Table VI: Clinical studies of levetiracetam (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetic neuropathy	Open	Levetiracetam, 250 mg od evening (titrated every 3-5 d up to 1500-6500 mg) x 5.5 (mean) mo	38	Levetiracetam was effective for the treatment of chronic neuropathic pain	3
Migraine	Open	Levetiracetam, up to 1500 mg po bid (titrated from 500 mg bid) x 3 mo	62	Levetiracetam was relatively well tolerated and may be an effective therapy for refractory migraine	4
Peripheral neuropathy	Open	Gabapentin, 300-2400 mg + Levetiracetam 500-1000 mg/d	10	Levetiracetam combined with gabapentin could be helpful in patients who respond only partially to gabapentin alone in the treatment of neuropathic pain	5
Migraine	Open	Levetiracetam, up to 1000 mg po bid (titrated from 250 mg od over 1 mo) x 3 mo + background medication	30	Levetiracetam may be an effective adjunct prophylactic therapy for refractory migraine	6

Memantine Hydrochloride



Memantine hydrochloride is an NMDA receptor antagonist under development in Europe and the U.S. by Merz, Neurobiological Technologies, Lundbeck and Forest, and in Japan by Suntory for the treatment of Alzheimer's disease (1-4). The product is also being developed by Forest and Neurobiological Technologies for the treatment of neuropathic pain.

Memantine has been shown to be highly effective in relieving pain in various animal models of neuropathic pain (5).

Neurobiological Technologies has announced that Forest will be conducting the second of two necessary trials for registration of memantine for the treatment of painful diabetic neuropathy. Neurobiological Technologies conducted the first trial in 400 patients with positive results. Forest is conducting an additional large-scale, multicenter, double-blind, placebo-controlled trial to assess the safety and efficacy of memantine in the treatment of diabetic neuropathy (6).

1. *Development of memantine in Japan extended to mild to moderate AD under new agreement*. DailyDrugNews.com (Daily Essentials) March 22, 2002.

2. *European approval of memantine for Alzheimer's disease recommended*. DailyDrugNews.com (Daily Essentials) Feb 26, 2002.

3. *Neurological drugs in Lundbeck's pipeline*. DailyDrugNews.com (Daily Essentials) Sept 20, 2001.

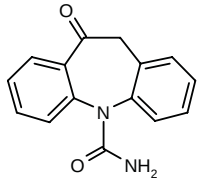
4. *Product developments announced by Forest*. DailyDrugNews.com (Daily Essentials) Feb 2, 2001.

5. Banerjee, P. *Beneficial effects of memantine, a moderate affinity uncompetitive NMDA receptor antagonist, in experimental models of neuropathic pain*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P06.122.

6. *Memantine to be evaluated in the treatment of diabetic neuropathy*. DailyDrugNews.com (Daily Essentials) Aug 3, 2001.

Original monograph - Drugs Fut 1976, 1(9): 427.

Oxcarbazepine



Oxcarbazepine is an antiepileptic drug marketed by Novartis as Trileptal® in over 50 countries which has also been approved for the treatment of trigeminal neuralgia.

A new process for the preparation of oxcarbamazepine has been reported: Reaction of 1-phenyl-2,3-dihydro-1*H*-indol-2-one (I) with NaOH in refluxing THF

gives 2-[2-(phenylamino)phenyl]acetic acid (II), which is condensed with dimethyl carbonate (III) by means of butyl lithium in the same solvent to yield 2-[2-[*N*-(methoxycarbonyl)-*N*-phenylamino]phenyl]acetic acid (IV). Cyclization of compound (IV) by means of polyphosphoric acid (PPA) at 100 °C, followed by treatment of the reaction mixture with hot methanol (65 °C) affords 10-methoxy-5*H*-dibenzo[*b,f*]azepine-5-carboxylic acid methyl ester (V), which is treated with NaOH in polyethyleneglycol at 100 °C to provide 10-methoxy-5*H*-dibenzo[*b,f*]azepine (VI). Reaction of (VI) with sodium cyanate in acetic acid gives 10-methoxy-5*H*-dibenzo[*b,f*]azepine-5-carboxamide (VII), which is finally treated with H_2SO_4 (1). Scheme 3.

In an open-label study, 10 patients with central neuropathic pain following spinal cord injury were given oxcarbazepine titrated to a maximum of 900 mg/day and maintained for 6 weeks. Patients who experienced moderate or better pain relief continued treatment titrated to a maximum dose of 1500 mg/day until completion of 9 weeks. Oxcarbazepine treatment was considered satisfactory by all 6 patients with allodynia in contrast to patients without allodynia (2). The results of this study and some of those that follow are summarized in Table VII.

A multicenter, randomized, double-blind, escalating-dose trial involving 48 treatment-naive patients with newly diagnosed trigeminal neuralgia compared the efficacy of oxcarbazepine (starting dose of 300 mg b.i.d. for 6-32 weeks) with carbamazepine (starting dose of 200 mg b.i.d. for 6-32 weeks). All oxcarbazepine-treated patients and 95% of the carbamazepine-treated patients had a 50% decrease in the number of attacks per week. A reduction of 2 days or more in the number of days with pain per week was seen in 96% of oxcarbazepine-treated patients as compared to 86% in the carbamazepine group. A successful rating in the global assessment of efficacy was reported for 96 and 91% of the patients in the oxcarbazepine and carbamazepine groups, respectively. No severe adverse events were reported and 68% of the oxcarbazepine-treated patients had an excellent rating in the global assessment of tolerability as compared to 52% in the carbamazepine group. The most frequent adverse events were tiredness, dizziness and vertigo for both groups (3).

Oxcarbazepine was compared to carbamazepine for the symptomatic treatment of new-onset trigeminal neuralgia in a randomized, double-blind study in 46 patients. Oxcarbazepine 300 mg b.i.d. and carbamazepine 200 mg b.i.d. were titrated to the most effective doses over 2-4 weeks and those doses were maintained for a further 4 weeks. The treatments demonstrated comparable efficacy in improving spontaneous and evoked pain (4).

Scheme 3: Synthesis of Oxcarbazepine

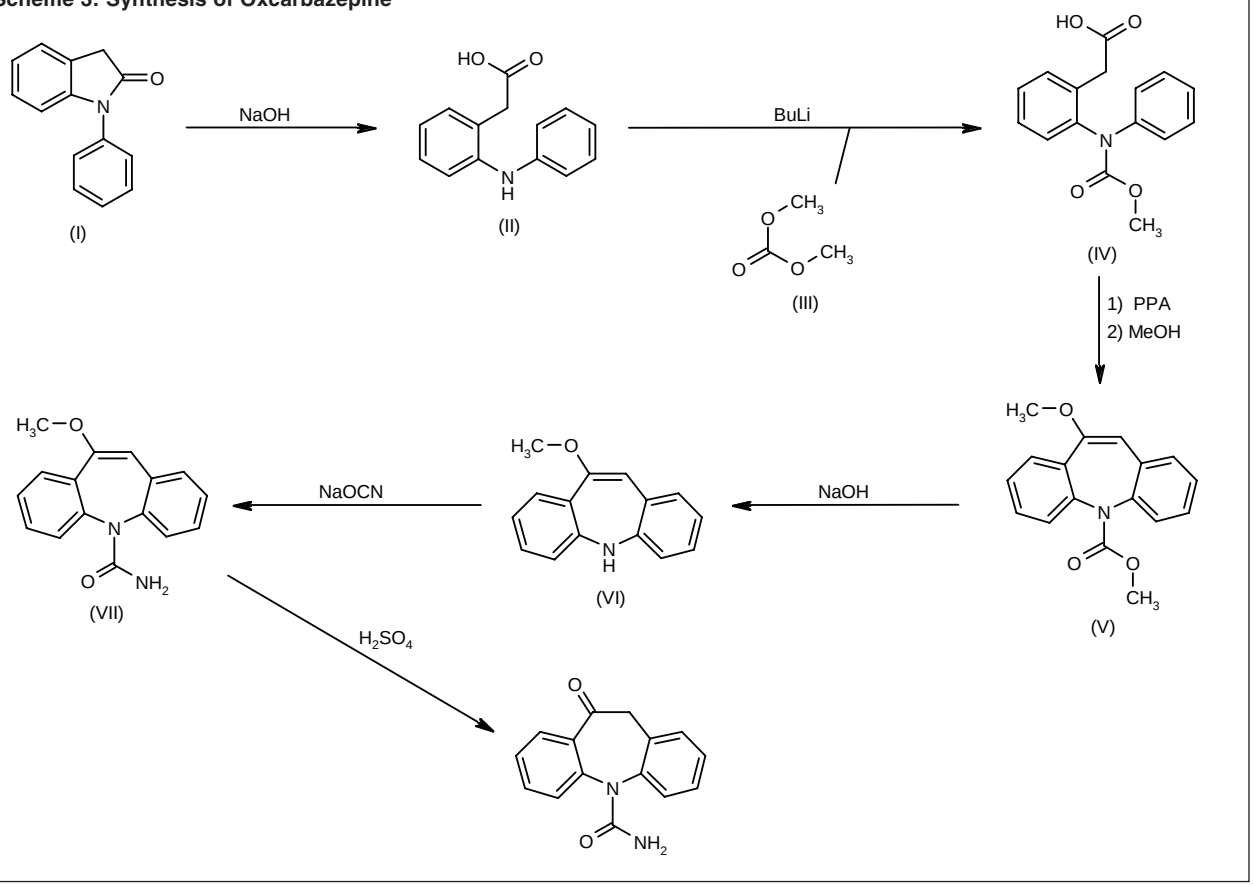


Table VII: Clinical studies of oxcarbazepine (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Spinal injury	Open	Oxcarbazepine, 900 mg/d po x 10 d → up to 1500 mg/d po x 9 wk	10	Oxcarbazepine reduced spinal cord injury-induced neuropathic pain in all patients with allodynia	2
Trigeminal neuralgia	Randomized, double-blind, multicenter	Oxcarbazepine, 300 mg bid (increased if needed) x 6-32 wk Carbamazepine, 200 mg bid (increased if needed) x 6-32 wk	48	Oxcarbazepine showed good tolerability and efficacy slighly better than or similar to carbamazepine in the treatment of patients with trigeminal neuralgia	3
Trigeminal neuralgia	Randomized, double-blind	Carbamazepine, 200 mg bid x 2-4 wk (titration) → 500 mg/d x 4 wk (n=22) Oxcarbazepine, 300 mg bid x 2-4 wk (titration) → 750 mg/d x 4 wk (n=24)	46	Oxcarbazepine showed tolerability and efficacy similar to carbamazepine in the treatment of patients with untreated trigeminal neuralgia	4
Trigeminal neuralgia	Open	Oxcarbazepine, 300 mg/d (up to 600-1800 mg/d) x 4 y (mean) (if no pain relief) → surgery (n=15)	21	Results showed that the mean time for recurrence of pain was significantly longer in patients surgically treated than those treated with oxcarbazepine	5
Trigeminal neuralgia	Randomized, double-blind, pooled data	Oxcarbazepine, 750 mg (naive) or 1050-1200 mg (refractory) (uptitrated for 4 wk) x 8 wk (n=69) Carbamazepin, 500mg (naive) or 700-900mg (refractory) (uptitrated for 4 wk) x 8 wk (n=61)	160	Similar efficacy was seen with oxcarbazepine and carbamazepine, although fewer side effects were observed in the oxcarbazepine-treated patients with trigeminal neuralgia	6
Cervical radiculopathy, lumbar radiculopathy, postherpetic neuralgia	Retrospective	Oxcarbazepine, 150 mg/d → 900 mg/d (if needed)	7	Preliminary results suggest that oxcarbazepine was well tolerated and effective in the treatment of neuropathic pain	7
Neuralgia	Open	Oxcarbazepine, 150-300 mg od evening x 3-5 d → up to 1200 mg (if needed) od evening x 10 mo	18	Preliminary results showed that oxcarbazepine was well tolerated and effective in relieving pain in patients with refractory complex regional pain syndrome	8
Neuralgia, radiculopathy	Open	Oxcarbazepine, 150-300 mg od evening x 3-5 d (if needed) up to 1200 mg od evening x 10 mo	18	Oxcarbazepine was well tolerated and effective in relieving neuropathic pain in patients with refractory radiculopaty	9
Diabetic neuropathy	Open	Oxcarbazepine, 75 mg bid x 4 wk (titration) → 600 mg bid (mean = 814 mg) x 4 wk	30	Preliminary results showed that oxcarbazepine was well tolerated and effective in improving pain in patients with diabetic neuropathy even at lower doses than those used in epilepsy	10
Neuralgia	Open, crossover	Oxcarbazepine, 150 mg bid x 3 d → 300 mg bid x 3 mo	4	Results suggested that oxcarbazepine is potentially effective in the treatment of neuropathic pain	11

Researchers prospectively followed for 13 years 15 patients with trigeminal neuralgia intractable to available drugs who were initially treated with oxcarbazepine 1200 ± 600 mg/day and subsequently with surgery. Oxcarbazepine was effective only in the short term, making surgical intervention necessary. Better outcomes were seen with all types of surgery (5).

Researchers completed a meta-analysis of 3 randomized, double-blind trials comparing oxcarbazepine and carbamazepine in a total of 130 patients with trigeminal neuralgia. Median daily doses were oxcarbazepine 750 mg and carbamazepine 500 mg for newly diagnosed patients; median daily doses for refractory patients were 1050-1200 mg and 700-900 mg, respectively. In these trials, oxcarbazepine was as effective as carbamazepine and was associated with fewer adverse events (6).

A retrospective study evaluated the administration of oxcarbazepine to 7 patients with pain and evidence of nerve injury who had previously been unsuccessfully treated with other analgesics. Oxcarbazepine at daily doses of 150-900 mg decreased the mean pain score without significant side effects, suggesting that this drug may be useful in the treatment of neuropathic pain related to peripheral nerve injury (7).

The efficacy of oxcarbazepine (up to 1200 mg/day) in the treatment of neuropathic pain refractory to gabapentin was assessed in 18 patients in an open-label trial. The results confirmed that oxcarbazepine is a valuable option for treating patients with complex regional pain syndrome refractory to gabapentin. The study also confirmed the good safety profile of the drug (8, 9).

An open-label, prospective trial reported improvement in pain scores, Clinician Global Impression of Change scores and quality of life scores in 30 patients with painful diabetic neuropathy after treatment with oxcarbazepine at a mean daily dose of 814 mg (10).

A group of researchers evaluated the efficacy of add-on therapy with 150 mg (later increased to 300 mg) of oxcarbazepine in 4 patients with idiopathic neuropathic pain. Pain, mood, productivity and sleep quality improved with the administration of oxcarbazepine (11).

1. Fünfschilling, P., Kaufmann, D., Lohse, O., Beutler, U., Zaugg, W. (Novartis AG; Novartis-Erfindungen VmbH). *Dibenzo[b,f]azepine derivs. and their preparation.* WO 0156992.

2. Jenkins, K., Kaplan, S.E., Leahy, L.F., Sang, C.N. *Oxcarbazepine in central neuropathic pain with allodynia following spinal cord injury*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 637.

3. Liebel, J. *Results of double-blind trial comparing oxcarbazepine (OXC) vs carbamazepine (CBZ) in newly diagnosed, untreated patients with trigeminal neuralgia*. 17th World Congr Neurol (June 17-22, London) 2001, Abst 02.01.

4. Beydoun, A., D'Souza, J. *Oxcarbazepine versus carbamazepine in patients with new-onset trigeminal neuralgia: Results of a double-blind comparative trial*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P06.116.

5. Zakrzewska, J.M., Patsalos, P.N. *Long-term cohort study comparing medical (oxcarbazepine) and surgical management of intractable trigeminal neuralgia*. Pain 2002, 95(3): 259.

6. Beydoun, A., Schmidt, D., D'Souza, J. *Meta-analysis of comparative trials of oxcarbazepine versus carbamazepine in trigeminal neuralgia*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 749.

7. Dreyer, M.D., Edwards, K., Norton, J. *Oxcarbazepine: Preliminary clinical experience in the treatment of neuropathic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 755.

8. Royal, M.A., Jenson, M., Bhakta, B., Gunyea, I., Movva, V., Ward, S. *An open-label trial of oxcarbazepine in patients with complex regional pain syndrome refractory to gabapentin*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 763.

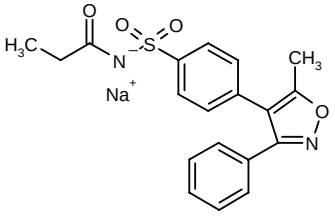
9. Ward, S., Royal, M., Jenson, M., Bhakta, B., Gunyea, I., Movva, V. *An open-label trial of oxcarbazepine in patients with radiculopathy refractory to gabapentin*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 765.

10. Carrazana, E., Beydoun, A., Kobetz, S., Constantine, S. *An open-label, prospective trial of oxcarbazepine in the treatment of painful diabetic neuropathy*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 751.

11. Hamza, M., Rowlingson, J.C. *Initial experience with oxcarbazepine in the treatment of idiopathic neuropathic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 756.

Original monograph - Drugs Fut 1986, 11(10): 844.

Parecoxib Sodium



The European Commission recently approved Pharmacia's parecoxib sodium (Dynastat™) as the first injectable COX-2-specific inhibitor for the short-term treatment of postoperative pain. Parecoxib received single marketing authorization for use in the 15 E.U. member states, which will be extended to Norway and Iceland. The first launch of parecoxib took place in the U.K. (1, 2).

The approval of parecoxib was based on studies involving patients undergoing various common surgeries, including hip and knee replacement, abdominal gynecological surgery, coronary artery bypass graft (CABG) surgery and third molar extraction with bone resection. In several studies, parecoxib afforded pain relief superior to low doses (4 mg i.v.) of morphine, while in others it effectively relieved pain when combined with morphine, improved patient satisfaction and reduced overall morphine use. The NDA was deemed not approvable by the FDA and Pharmacia expects to file a supplement later this year or early next year (3).

The pharmacokinetics, safety and tolerability of intramuscular parecoxib (1, 2, 5, 10, 20 or 40 mg) were determined in a randomized, double-blind, placebo-controlled study in 56 healthy male volunteers. The maximum tolerated single i.m. dose was found to be 40 mg (4).

A randomized, double-blind, placebo-controlled trial in 12 healthy volunteers was conducted to evaluate the impact of parecoxib (40 mg i.v.) on the pharmacokinetic and clinical effects of alfentanil (15 μg/kg) and fentanyl (5 μg/kg). Parecoxib was not found to alter the disposition of the other treatments or their clinical effects and the trial results suggested that parecoxib does not cause significant CYP3A4 interactions (5).

In a randomized, double-blind study, analgesia with parecoxib 20 and 40 mg i.v. was compared to that with placebo, ketorolac 15 mg i.v. or morphine 4 mg i.v. in 204 patients who had undergone total hip arthroplasty. The postoperative pain of these patients was similarly controlled by single doses of parecoxib and ketorolac, which

Table VIII: Clinical studies of parecoxib sodium (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hip arthroplasty, postoperative pain	Randomized, double-blind	Parecoxib, 20 mg iv → (6 h later) 20 mg bid iv x 5 d Parecoxib, 40 mg iv → (6 h later) 40 mg bid iv x 5 d Ketorolac, 15 mg iv → (6 h later) 15 mg q.i.d. iv Morphine, 4 mg iv → (6 h later) continue to P20, P40 or K Placebo → (6 h later) continue with P20, P40 or K	204	Single doses of parecoxib 20 and 40 mg had a similar effect as ketorolac 15 mg and greater analgesic efficacy than placebo and morphine 4 mg in pain after total hip arthroplasty	6
Bunion operation, postoperative pain	Double-blind, multicenter	Parecoxib, 20 mg iv (30-45 min before surgery) Parecoxib, 40 mg iv (30-45 min before surgery) Placebo sd	50	Preliminary results showed that preoperative administration of parecoxib was safe, well tolerated and provided significantly greater analgesic efficacy than placebo in patients who underwent bunionectomy	7
Laparotomy, postoperative pain	Randomized, double-blind	Parecoxib, 20 mg iv bid + Morphine, 1.2 mg (on demand) Parecoxib, 40 mg iv bid + Morphine, 1-2 mg (on demand) Placebo + Morphine, 1-2 mg (on demand)	216	Parecoxib showed an opioid-sparing effect when it was administered immediately after surgery and prior to the first postoperative dose of morphine	8
Hysterectomy, laparotomy, myomectomy	Randomized, double-blind	Parecoxib, 20 mg iv → (24 h later) continue with P20, P40 or K→ Parecoxib, 40 mg iv → (24 h later) continue with P20, P40 or K Ketorolac, 30 mg iv → (24 h later) continue with P20, P40 or K Morphine, 4 mg iv → (24 h later) continue with P20, P40 or K Placebo → (24 h later) continue with P20, P40 or K	208	Parecoxib 40 mg sd was well tolerated and had a similar effect as ketorolac but greater analgesic efficacy than placebo, parecoxib 20 mg and morphine 4 mg in major gynecologic postoperative pain	11
Knee arthroplasty, postoperative pain	Randomized, double-blind, multicenter	Parecoxib, 20 mg iv bid x 48 h (n=65) Parecoxib, 40 mg iv bid x 48 h (n=67) Placebo x 48 h (n=63)	195	Parecoxib was well tolerated and showed opioid sparing effects, decreasing postoperative consumption of morphine, in patients undergoing knee replacement surgery. Morphine taken in combination with parecoxib had a synergestic effect	12
Dental operation, postoperative pain	Randomized, double-blind	Parecoxib, 20 mg iv (30-45 min before surgery) (n=56) Parecoxib, 40 mg iv (30-45 min before surgery) (n=56) Parecoxib, 80 mg iv (30-45 min before surgery) (n=56) Placebo (30-45 min before surgery) (n=56)	224	Preoperative administration of parecoxib was safe and effective in reducing or eliminating postoperative pain in patients undergoing third molar extractions	13

were significantly more effective than placebo or morphine (6). The results of this study and some of those that follow are summarized in Table VIII.

Single i.v. doses of parecoxib 20 or 40 mg or placebo were administered to 50 bunionectomy patients in a multicenter, double-blind study. The treatment was significantly superior to placebo in providing postoperative analgesia, was well tolerated and did not increase the risk of bleeding (7).

Researchers evaluated morphine consumption in 216 women who had undergone lower abdominal gynecological surgery and were treated with parecoxib 20 or 40 mg i.v. after surgery and before morphine administration. In this double-blind study, patients given parecoxib consumed less morphine than placebo-treated patients (8).

Results were reported from a phase III study involving 175 patients, demonstrating that parecoxib significantly reduced the use of morphine following total hip replace-

ment surgery while improving overall pain relief. In the multicenter, placebo-controlled, double-blind study, patients receiving a 40-mg dose of parecoxib required 39% less morphine in the 24 h following hip replacement surgery compared to placebo-treated patients. Patients were randomly assigned to receive parecoxib 20 mg (n = 60), parecoxib 40 mg (n = 53) or placebo (n = 62). The overall incidence of adverse events was similar among groups, although significantly fewer patients in the high-dose parecoxib group reported fever and/or vomiting than in the placebo group. These patients reported higher pain intensity difference scores at most or all assessment points, as well as in measures of overall well-being. A second multicenter, double-blind phase III trial evaluated the control of pain following total knee replacement in 208 patients using single i.v. doses of parecoxib, morphine or ketorolac. The analgesic efficacy of parecoxib 40 mg proved comparable to ketorolac 30 mg and superior to morphine 4 mg at most time points. Furthermore, 80% of patients who received the 40-mg dose of parecoxib rated their pain medication as good or excellent, compared with approximately 70% of ketorolac patients and 45% of morphine patients (9).

A randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 7-day endoscopic trial involving 17 healthy elderly (66-75 years) subjects compared the safety and tolerability of parecoxib (10 mg i.v. b.i.d. for 7 days) with naproxen (500 mg b.i.d.) or placebo (for 2 days) followed by ketorolac (15 mg q.i.d. i.v. for 5 days). Endoscopy was performed at baseline and after 7 days of treatment. Ulcers were detected in patients treated with ketorolac (4/4 subjects), naproxen (2/4 subjects) and placebo (2/5), but not in those receiving parecoxib. Multiple gastric ulcers or combined gastric and duodenal ulcers were observed in 4 subjects in the ketorolac group and 1 subject in the naproxen group. The study was terminated due to the high incidence of gastroduodenal ulcers (10).

In a randomized, double-blind, placebo- and active-controlled study, 208 women who had undergone total abdominal hysterectomy or myomectomy were administered intravenous doses of parecoxib (20 or 40 mg), placebo, ketorolac (30 mg) or morphine (4 mg). Parecoxib 40 mg and ketorolac 30 mg demonstrated similar efficacy and were better than the other treatments in reducing postoperative pain (11).

A total of 195 patients who underwent knee replacement surgery received self-administered morphine and i.v. parecoxib 20 or 40 mg b.i.d. postoperatively. Better analgesia was achieved when parecoxib was combined with morphine than with morphine alone and the addition of parecoxib significantly reduced morphine consumption (12).

A randomized, double-blind, placebo-controlled study examined the administration of single i.v. doses of parecoxib 20, 40 and 80 mg before oral surgery in 224 patients. Fewer adverse events and greater analgesic efficacy were seen with parecoxib as compared with placebo. The 40- and 80-mg parecoxib doses demonstrated equivalent efficacy (13).

1. *E.U. approval for Dynastat in postoperative pain*. DailyDrugNews.com (Daily Essentials) April 12, 2002.

2. *Injectable COX-2-specific painkiller launched for the first time*. DailyDrugNews.com (Daily Essentials) May 2, 2002.

3. *Pharmacia receives nonapprovable letter from FDA for analgesic product*. DailyDrugNews.com (Daily Essentials) July 17, 2001.

4. Karim, A., Laurent, A., Slater, M.E., Kuss, M.E., Qian, J., Crosby-Sessoms, S.L., Hubbard, R.C. *A pharmacokinetic study of intramuscular (IM) parecoxib sodium in normal subjects*. J Clin Pharmacol 2001, 41(10): 1111.

5. Kharasch, E., Ibrahim, A., Karim, A., Feldman, J. *Effects of parecoxib, a parenteral COX-2 specific inhibitor, on the pharmacokinetics and clinical effects of fentanyl and alfentanil*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-450.

6. Hubbard, R.C., Stultberg, B.N., Torri, S., Talwalkker, S., Kuss, M.E. *The COX-2 specific inhibitor parecoxib sodium is effective in treating post-operative pain in total hip arthroplasty patients*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-807.

7. Hubbard, R.C., Teeney, S., Grossman, E.H., Kuss, M.E., Talwalker, S. *Preoperative administration of parecoxib sodium effectively reduced post-operative pain in bunionectomy patients*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-812.

8. Wender, R.H., Desai, P.M., Snabes, M.C., Talwalker, S.C., Kuss, M.E., Hubbard, R.C. *Parecoxib sodium demonstrates opioid sparing effects in post-laparotomy surgical patients*. Fertil Steril 2001, 76(3, Suppl. 1): Abst P-325.

9. *Phase III data show Pharmacia's parecoxib reduces morphine use following surgery*. DailyDrugNews.com (Daily Essentials) April 24, 2001.

10. Harris, S.I., Kuss, M., Hubbard, R.C., Goldstein, J.L. *Upper gastrointestinal safety evaluation of parecoxib sodium, a new parenteral cyclooxygenase-2-specific inhibitor, compared with ketorolac, naproxen, and placebo*. Clin Ther 2001, 23(9): 1422.

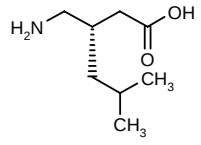
11. Bikhazi, G.B., Bajwa, Z.H., Snabes, M.C., Lecomte, D.L., Talwalker, S.C., Hubbard, R.C. *Parecoxib sodium effectively treats post-laparotomy pain*. Fertil Steril 2001, 76(3, Suppl. 1): Abst P-481.

12. Hubbard, R.C., Camu, F., Kuss, M.E., Talwalker S., Beecher, T. *The COX-2 specific inhibitor parecoxib sodium is an effective opioid-sparing agent in patients undergoing knee replacement surgery*. Annu Meet Am Soc Anesthesiol (ASA) (Oct 13-17, New Orleans) 2001, Abst A-808.

13. Desjardins, P.J., Grossman, E.H., Kuss, M.E., Talwalker, S., Dhadda, S., Baum, D., Hubbard, R.C. *The injectable cyclooxygenase-2-specific inhibitor parecoxib sodium has analgesic efficacy when administered preoperatively*. Anesth Analg 2001, 93(3): 721.

Original monograph - Drugs Fut 2001, 26(2): 133.

Pregabalin

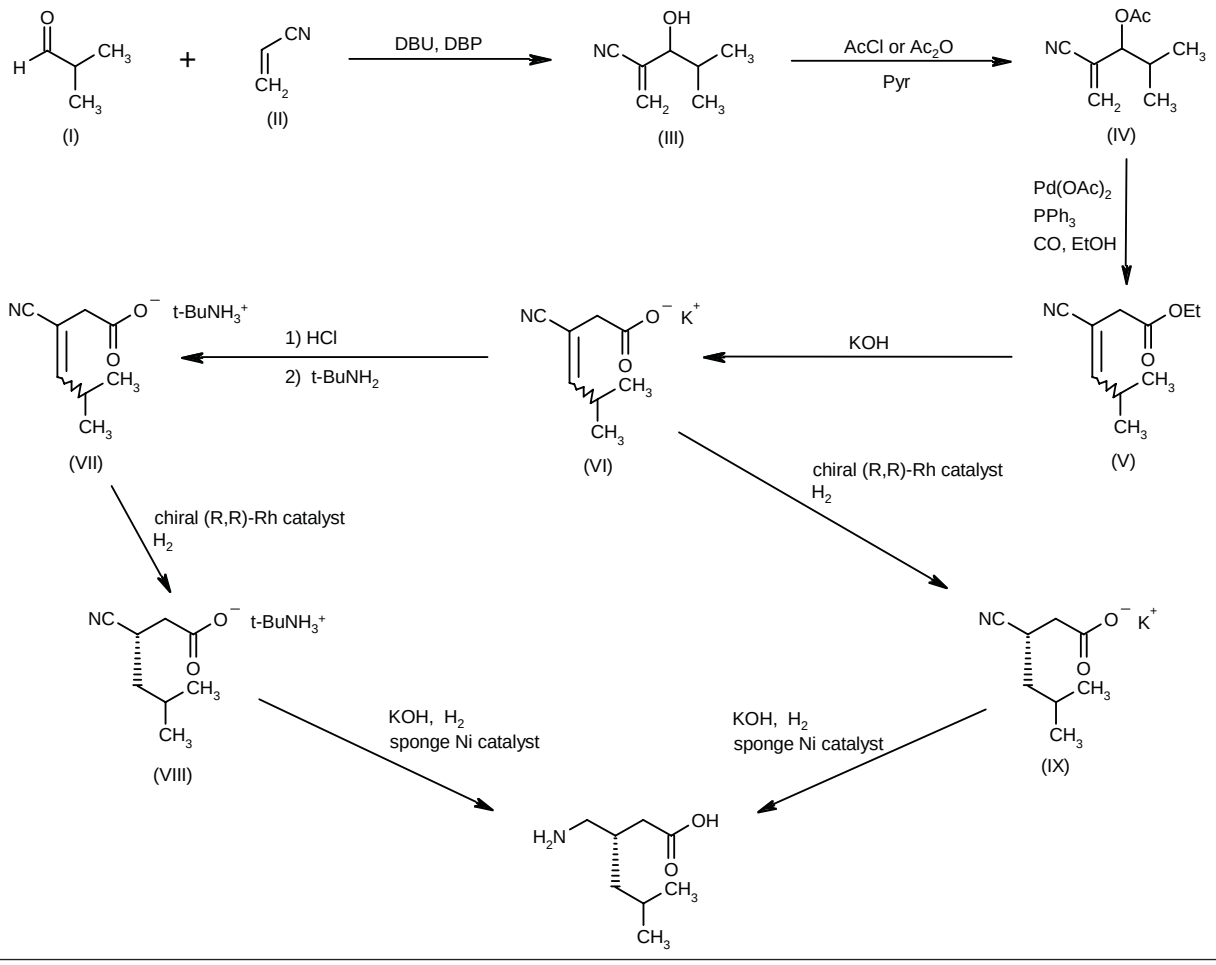


Pregabalin (PD-144723, CI-1008) is under late-stage development at Pfizer for the treatment of neuropathic pain, epilepsy, a variety of anxiety disorders and chronic pain conditions for which there are only limited treatment options.

An asymmetric synthesis of pregabalin has been reported: Condensation of isobutyraldehyde (I) with acrylonitrile (II) by means of DBU and 2,6-di-*tert*-butyl-4-methylphenol (DBP) gives 3-hydroxy-4-methyl-2-methylenepentanenitrile (III), which is acylated with AcCl or Ac_2O and pyridine to yield the acetate (IV). The carboxylation of (IV) by means of $Pd(OAc)_2$, PPh_3, CO and EtOH affords 3-cyano-4-methyl-3-hexenoic acid ethyl ester (V), which is hydrolyzed with KOH in THF/water to provide the corresponding carboxylic acid potassium salt (VI). Acidification of (VI) with HCl, followed by reaction with *tert*-butylamine gives the corresponding salt (VII), which is reduced with H_2 over a chiral (*R*,*R*)-rhodium catalyst [(*R*,*R*)-Rh] in THF/water to yield (*S*)-3-cyano-5-methylhexanoic acid butylammonium salt (VIII). Finally, the CN group of (VIII) is reduced with H_2 over a sponge-Ni catalyst in basic (KOH) ethanol (1). Scheme 4.

Results of a study of the inhibitory effects of gabapentin and pregabalin on K^+-evoked, Ca^{2+}-dependent release of neurotransmitters from discrete rat CNS regions suggested that the drugs selectively modulate the presynaptic terminal voltage-sensitive Ca^{2+} channel function of multiple neurotransmitter systems in many CNS regions (2).

Scheme 4: Synthesis of Pregabalin



Intracolonic (i.c.) and intrathecal (i.t.) glutamate was evaluated for its effect on pain by assessing its influence on the spontaneous occurrence of abdominal contractions in rats. The same study evaluated antagonism by orally and intrathecally administered pregabalin on i.c. and i.t. glutamate-induced abdominal cramps. In one set of experiments, i.c. glutamate (4 mg/kg) was administered to rats treated with pregabalin and its vehicle either p.o. (30 mg/kg) 1 h before or i.t. (300 μg/kg) 10 min after glutamate. From 1-2 h after i.c. glutamate administration, abdominal spike bursts were increased significantly. In a second set of experiments, administration of pregabalin (either 30 mg/kg p.o. or 300 μg/kg i.t.) was followed by i.t. administration of glutamate (40 μg/kg). Glutamate administered i.t. resulted in an 86% increase in abdominal spike bursts lasting longer than 2 h, although neck muscle was unaffected. Both p.o. and i.t. pregabalin inhibited the effects of i.c. and i.t. glutamate. Neither i.t. nor p.o. pregabalin affected the basal number of abdominal cramps noted after vehicle administered i.t. or i.c (3).

A study which investigated the effect of pregabalin on visceral pain has been reported. Electrodes were implanted or not on the external abdominal muscle of male SD rats. After 2 weeks, pregabalin 30 mg/kg or water was administered, and a latex balloon was inserted through the anus into the rectocolic segment of the animals. Pregabalin was found to reduce the number of abdominal contractions in response to the first and second colorectal distensions as compared with controls. Pregabalin also reduced the heightened AUC during the second distension by 13% in comparison to controls. In addition to inhibiting visceral pain from repeated colorectal distension and inhibiting visceral hypersensitivity, pregabalin blunted L6-S1 spinal cord neuronal activation induced by repeated colorectal distension (4).

A study examined the population pharmacokinetics of pregabalin in healthy volunteers, patients with renal impairment and patients with chronic pain. The results demonstrated that the pharmacokinetics of the drug are linear and that oral clearance is related to creatinine clearance in both healthy volunteers and patients with chronic pain. Dose adjustments did not appear necessary under conditions of concomitant administration of insulin, diuretics or oral antidiabetics (5).

A study conducted in 6 healthy male volunteers showed that pregabalin was predominantly eliminated by renal excretion and its metabolism was negligible. Following p.o. administration of [^{14}C]-pregabalin (100 mg), total radioactivity was mainly recovered in urine (92% *vs.* < 0.1% for feces). In urine collected during the first 48 h postdose, radioactivity was mainly due to unchanged pregabalin (89.9%). Minor components detected included the *N*-methylated metabolite (0.9%) and an unidentified agent (0.4%). Similarly, unchanged pregabalin accounted for most of the radioactivity in plasma (6).

Pregabalin 300 mg t.i.d. was evaluated in a randomized, double-blind, placebo-controlled study in patients with diabetic peripheral neuropathy. Treatment for 8 weeks indicated that the regimen was safe and effective, with significantly more patients in the pregabalin group experiencing a reduction of at least 50% in pain compared to the placebo group (7). The results of this study and some of those that follow are summarized in Table IX.

The efficacy and safety of pregabalin (300 mg t.i.d.) for relieving pain were determined in 146 patients suffering from painful diabetic neuropathy. Compared to placebo, pregabalin improved the mean pain score and the number of responders, with a good safety profile (8).

The relationship between exposure to pregabalin and efficacy in the treatment of postherpetic neuralgia was investigated by a group using data from 3 double-blind studies. It was found that an E_{max} model using average concentration as the measure of exposure best described the efficacy of pregabalin, which rapidly reduced pain in such patients in a dose- and concentration-dependent manner (9).

Two double-blind, parallel-group studies conducted in 557 diabetic patients with neuropathic pain examined the relationship between pregabalin exposure (dose and concentration) and response following multiple dosing (75-600 mg/day). Data were again best described by an E_{max} model. Compared to placebo, 300 mg/day of pregabalin decreased the pain score by approximately 1 point. When the dose was increased up to 600 mg, the pain score decreased by approximately 40% (10).

Doses of pregabalin of 50 and 300 mg were compared to placebo and ibuprofen 400 mg in a randomized, double-blind trial in 198 patients with postoperative dental pain. Pregabalin 300 mg demonstrated superior efficacy to placebo and the 50-mg pregabalin dose on all parameters. Pregabalin 300 mg also produced longer lasting analgesia than ibuprofen and received the highest score on the patient global impression of study medication (11).

A double-blind study in patients with postherpetic neuralgia compared pregabalin (300 or 600 mg/day) to placebo over 8 weeks in terms of mean pain score from the patient's daily pain diary, the primary efficacy measure, and the SF-McGill Pain Questionnaire (SF-MPQ). Significant improvement was seen at 1 week in pregabalin-treated patients for both the primary endpoint and the SF-MPQ sensory, affective and total scores, visual analogue scale and present pain intensity patient ratings. These effects were maintained for the duration of the study (12).

Pfizer has restricted the use of pregabalin for certain patients in clinical trials following discussions with the FDA. The restriction is the result of the FDA's analysis of

Table IX: Clinical studies of pregabalin (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Diabetic nephropathy	Randomized, double-blind	Pregabalin, 300 mg tid x 8 wk (n=76) Placebo (n=70)	146	Pregabalin showed a safe, well tolerated and effective profile in patients with diabetic neuropathic pain and associated sleep disorder	7
Diabetic autonomic neuropathy	Randomized, double-blind, multicenter	Pregabalin, 300 mg tid x 8 wk (n=76) Placebo (n=70)	146	Pregabalin 300 mg daily was safe and effective in improving pain in diabetic neuropathy	8
Postherpetic neuralgia	Double-blind, pooled data	Pregabalin, 75, 150, 300 or 600 mg/d	661	Pregabalin decreased pain in patients with postherpetic neuralgia in a dose-dependent manner	9
Diabetic nephropathy	Double-blind, pooled data	Pregabalin, 75, 150, 300 or 600 mg Placebo	557	Pregabalin decreased pain score versus placebo in neuropathic pain, showing highest responses with the 600 mg dose	10
Postoperative pain of tooth extraction	Randomized, double-blind	Pregabalin, 50 mg po (n=49) Pregabalin, 300 mg po (n=50) Ibuprofen, 400 mg po (n=49) Placebo (n=50)	198	Pregabalin could be an effective analgesic with a longer duration of action in patients with postoperative dental pain	11
Neuralgia	Randomized, double-blind	Pregabalin, 300-600 mg/d (depending on creatinine clearance) x 8 wk Placebo		Pregabalin was effective in improving pain in postherpetic neuralgia based on the daily pain diary and SF-MPQ questionnaire	12

previously submitted results from a lifetime mouse study that showed an increased incidence of a specific tumor type. It is not known whether these results are applicable to humans, since pregabalin is not a chemical mutagen and not genotoxic in preclinical studies. A similar lifetime dosing study in rats did not show increases in any tumor type, nor were negative results seen in any other toxicological screen or study. The submission of an NDA seeking FDA approval for pregabalin for the treatment of neuropathic pain and epilepsy, scheduled for late 2002, is expected to proceed as planned (13, 14).

1. Burk, M.J. et al. (Pfizer Inc.). *Asymmetric synthesis of pregabalin*. WO 0155090.

2. Donovan, C.M., Dooley D.J., Pugsley, T.A. *Gabapentin and pregabalin modulate K^+-evoked [^{3}H]-neurotransmitter release from discrete rat CNS regions*. Soc Neurosci Abst 2001, 27: Abst 711.6.

3. Eutamene, H., Theodorou, V., Toulouse, M., Chovet, M., Bueno, L. *Pregabalin acts centrally at post synaptic spinal level on glutamate-induced abdominal cramps*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1698

4. Million, M., Wang, L., Maryanov, T., Coutinho, S., Mayer, E., Tache, Y. *Oral pregabalin reduces repeated colorectal distention (CRD)-induced visceral pain and lumbosacral spinal cord neuronal activation in rats*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 29.

5. Corrigan, B.W., Burger, P., Bockbrader, H.N. *Population pharmacokinetics of pregabalin in healthy volunteers, renally impaired patients, and patients with chronic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 786.

6. Corrigan, B.W., Pool, W.F., Posvar, E.L., Strand, J.C., Alvey, C.W., Radulovic, L.L., Bockbreder, H.N. *Metabolic disposition of pregabalin in healthy volunteers*. Clin Pharmacol Ther 2001, 69(2): Abst PI-68.

7. Glessner, C., Sharma, U., Jacobellis, D., Moore, J., Lamoreaux, L.L., Poole, R.M. *Pregabalin relieves pain and reduces pain interference with sleep in patients with diabetic neuropathy*. Diabetes 2001, 50(Suppl. 2): Abst 753-P.

8. Sharma, U., Glessner, C., Moore, J., LaMoreaux, L.K., Garofalo, E.A., Poole, R.M. *Pregabalin efficacious for relief of painful diabetic neuropathy*. 54th Annu Meet Am Acad Neurol (April 13-20, Denver) 2002, Abst P06.126.

9. Corrigan, B.W., Frame, B., Burger, P., Poole, R.M., Bockbrader, H.N. *An analysis of exposure response data for pregabalin: A novel therapy for the treatment of postherpetic neuralgia*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 682.

10. Corrigan, B.W., Hermann, D., Burger, P., Miller, R., Blockbrader, H.N., Poole, R.M., Lalonde, R., Mandema, J. *An analysis of exposure response data for pregabalin: A novel therapy for the treatment of diabetic neuropathic pain*. Clin Pharmacol Ther 2001, 69(2): Abst PI-69.

11. Hill, C.M., Balkenohl, M., Thomas, D.W., Walker, R., Mathé, H., Murray, G. *Pregabalin in patients with postoperative dental pain*. Eur J Pain 2001, 5(2): 119.

12. Corbin, A.E., Young, J.P., LaMoreaux, L., Sharma, U., Garofalo, E.A., Poole, R.M. *Pregabalin reduces pain in patients with postherpetic neuralgia: Supportive data from SF-McGill Pain Questionnaire (SF-MPQ)*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 785.

13. *Industry leader Pfizer expects growth driven by broad and deep pipeline*. DailyDrugNews.com (Daily Essentials) Jan 21, 2002.

14. *Use of pregabalin restricted in certain clinical trial patients*. DailyDrugNews.com (Daily Essentials) Feb 13, 2001.

Original monograph - Drugs Fut 1999, 24(8): 862.

Rhenium Re-186 Etidronate

Rhenium Re-186 etidronate injection ([186Re]-HEDP) is a therapeutic radiopharmaceutical under development by Mallinckrodt for the palliation of pain associated with metastatic bone cancers.

In a randomized study, 50 patients with painful multifocal bone metastases from breast cancer were treated with [89Sr]-chloride 148 MBq or [186Re]-HEDP 1406 MBq. Both treatments were effective, with global response rates of 84 and 92% in the [89Sr]-chloride and [186Re]-HEDP groups, respectively. [186Re]-HEDP demonstrated a significantly faster onset of action (1). The results of this study and some of those that follow are summarized in Table X.

In a multicenter observational study, 818 patients with bone pain originating from metastases of prostate cancer were treated with a single i.v. dose of either [89Sr]-chloride (148 MBq) or [186Re]-HEDP (1295 MBq). Responses were good or excellent in 33.3 and 26.4% of patients, respectively. The radiopharmaceuticals demonstrated similar efficacy in pain palliation and toxicity, in both first treatments and retreatments (2, 3).

Pain relief was assessed in 37 patients with prostate cancer and metastatic bone pain who received [186Re]-HEDP 1295-3515 MBq. The treatment was effective in providing pain relief, with 54% of patients achieving a response (4).

The efficacy of [186Re]-HEDP (1295-2960 MBq) was evaluated in a double-blind, placebo-controlled study in 111 prostate cancer patients with metastatic bone pain. According to pain assessment criteria (pain intensity, medication index and daily activities), treatment with [186Re]-HEDP had a significant effect on palliation of metastatic bone pain associated with prostate cancer (5).

A study conducted in 29 patients undergoing radionuclide therapy for palliation of bone pain used a new scintigraphic quantification technique to separately measure bone uptake and soft tissue retention of [153Sm]-EDTMP (37 MBq) and [186Re]-HEDP (1295 MBq). The mean bone uptake at 3 and 24 h after injection of [186Re]-HEDP was 13.7 ± 8.6 and 21.8 ± 9% of initial whole-body activity, respectively, and 29.2 ± 15.5 and 47.7 ± 11.2%, respectively, after injection of [153Sm]-EDTMP. Soft tissue activity at 3 and 24 h following [186Re]-HEDP injection was 49.4 ± 16.9 and 12.8 ± 5.4%, respectively, compared to 38.4 ± 14.5 and 12.7 ± 4.7%, respectively, for [153Sm]-EDTMP. Urinary excretion for [186Re]-HEDP was 36.9 ± 14.4% at 3 h and 65.3 ± 12.8% at 24 h postinjection; these values for [153Sm]-EDTMP were 32.3 ± 12.9 and 39.5 ± 13.8%, respectively. It was concluded that results obtained using this method, which measures the region of interest, correlated well with conventional 24-h whole-body retention measurements. The new method offers the advantage that bone uptake and soft tissue retention can be calculated separately (6).

Patients (n = 8) with painful multifocal arthritis who had failed treatment with standard medication were treated with [186Re]-HEDP at a dose of 570 MBq. A single injection of the radionuclide resulted in an improvement in disease activity in 6 of 8 patients, which lasted 2-7 months (7).

Table X: Clinical studies of rhenium Re-186 etidronate (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Bone pain of breast cancer metastases	Randomized, open	Re-186 etidronate, 1406 MBq iv (n=25) Strontium-89 chloride, 148 MBq iv (n=25)	50	Re-186 etidronate and strontium-89 chloride were safe and effective in relieving bone pain in patients with breast cancer, with the latter showing a significantly faster onset of pain relief	1
Bone pain of prostate cancer metastases	Multicenter	Re-186 etidronate, 1295 MBq (35 mCi) iv sd (n=57) Strontium-89 chloride, 148 MBq (4 mCi) iv sd (n=452)	510	Re-186 etidronate did not seem to prolong life, although in some cases scintigraphic regression of bone metastases was observed. Both treatments were similar in efficacy and toxicity	3
Bone pain of cancer metastases		Re-186 etidronate, 1295 MBq/kg iv (n=11) Lexidronam Sm-153, 37 MBq/kg iv (n=18)	29	Results show higher soft tissue retention and urinary excretion but lower bone uptake with Re-186 etidronate than lexidronam Sm-153	6
Arthritis	Open	Re-186 etidronate, 570 MBq (15.4 mCi) iv sd	7	Systemic low-dose treatment with Re-186 etidronate was effective in relieving pain and improving disease activity in patients with polyarthritis	7

1. Sciuto, R., Festa, A., Pasqualoni, R., Semprebene, A., Rea, S., Bergomi, S., Maini, C.L. *Metastatic bone pain palliation with 89-Sr and 186-Re-HEDP in breast cancer patients*. Breast Cancer Res Treat 2001, 66(2): 101.

2. Piffanelli, A., Dafermou, A., Giganti, M., Colamussi, P., Pizzocaro, C., Bestagno, M. *Radionuclide therapy for painful bone metastases*. Q J Nucl Med 2001, 45(1): 100.

3. Dafermou, A., Colamussi, P., Giaganti, M., Cittanti, C., Bestagno, M., Piffanelli, A. *A multicentre observational study of radionuclide therapy in patients with painful bone metastases of prostate cancer*. Eur J Nucl Med 2001, 28(7): 788.

4. Quirijnen, J.M.S.P., Han, S.H., Zonnenberg, B.A., De Klerk, J.M.H., van het Schip, A.D., van Dijk, A., ten Kroode, H.F.J., Blijbam, G.H., van Rijk, P.P. *Efficacy of rhenium-186-etidronate in prostate cancer patients with metastatic bone pain*. J Nucl Med 1996, 37(9): 1511.

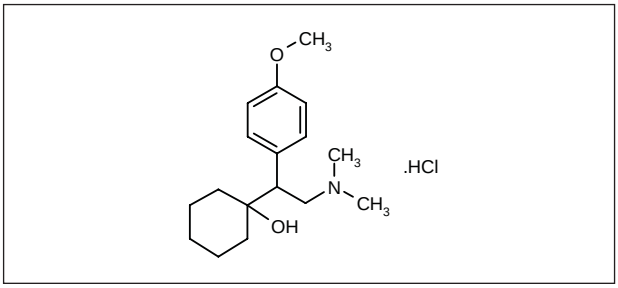
5. Zonnenberg, B.A., Han, S., Tan, S., Derksen, B., De Klerk, J., van Rijk, P. *Efficacy of rhenium-186-HEDP in prostatic cancer patients with metastatic bone pain: A placebo controlled study*. Proc Am Soc Clin Oncol 2001, 20(Part 2): Abst 2416.

6. Brenner, W., Kampen, W.U., Kampen, A.M., Henze, E. *Skeletal uptake and soft-tissue retention of Re-186-HEDP and Sm-153-EDTMP in patients with metastatic bone disease*. J Nucl Med 2001, 42(2): 230.

7. Palmedo, H., Rockstroh, M., Bangard, M., Schliefer, K., Risse, J., Menzel, C., Blersack, H.-J. *Painful multifocal arthritis: Therapy with rhenium 186 hydroxyethylidenediphosphonate (^{186}Re- HEDP) after failed treatment with medication – Initial results of a prospective study*. Radiology 2001, 221(1): 256.

Original monograph - Drugs Fut 1993, 18(6): 520.

Venlafaxine Hydrochloride



The antidepressant venlafaxine hydrochloride (Efexor®, Effexor®; Wyeth Pharmaceuticals) inhibits 5-HT reuptake and to a lesser extent noradrenaline reuptake. The compound is being evaluated for several new indications, including the treatment of pain states.

In a randomized, double-blind, placebo-controlled trial of analgesia with oral venlafaxine, 16 healthy volunteers received the study drug at a dose of 37.5 mg every 12 h for 4 doses. Pain tests were conducted before and 3 h after the second and fourth doses. The threshold at which repetitive electrical sural nerve stimulations cause pain summation was increased by venlafaxine, as was the pain tolerance threshold for single sural nerve stimulation (1). The results of this study and some of those that follow are summarized in Table XI.

Erythromelalgia is a rare disorder characterized by hot, red, intensely burning and painful feet or hands with occasional involvement of the face and ears which has long remained a diagnostic and therapeutic enigma. Recent research suggests that the manifestations of erythromelalgia are caused by constriction of some precapillary sphincters while arteriovenous shunts remain open. The result is an increase in total perfusion and a deficiency in nutritive perfusion, which leads to the development of hypoxia and hyperemia in affected skin; the products of tissue hypoxia trigger increased local blood flow, worsening the redness, warmth and pain. Pharmacological treatment of the disorder is of uncertain benefit since patient responses are inconsistent, suggesting the possibility of multiple subtypes, and no randomized trials have been conducted. The most useful oral medications for erythromelalgia to date are gabapentin, venlafaxine, diltiazem, sertraline, amitriptyline, imipramine, paroxetine, fluoxetine and some antihistamines (diphenhydramine, cyproheptadine), usually started at low doses. However, success has been extremely variable. A recent pilot study involving 7 patients with primary erythromelalgia demonstrated the efficacy and safety of the antidepressant venlafaxine hydrochloride at a dose of 37.5 mg p.o. b.i.d for 6-24 months. Treated patients had significant improvements in signs and symptoms within 2 weeks of treatment and continued benefit for the duration of the study. It is suggested that, by virtue of its dual inhibitory activity against 5-HT and noradrenaline reuptake, venlafaxine may improve the underlying microvascular dysfunction. A double-blind, placebo-controlled trial is under way to confirm these positive preliminary results (2, 3).

A 39-year-old patient with neuropathic back pain was successfully switched from amitriptyline, desipramine and imipramine treatment to extended-release venlafaxine 75 mg once daily. Pain relief was found to be equivalent to that with the tricyclic antidepressants but without the adverse effects (4).

A trial assessed the effects of 37.5-75 mg/day venlafaxine in 13 patients with well-controlled type 2 diabetes and painful peripheral polyneuropathy of the lower extremities. The investigators found an 82% decrease in the neuropathic pain scale score after 8 weeks of treatment. This effect was independent of mood (5).

A double-blind, randomized, placebo-controlled, crossover study was conducted to compare the efficacy and tolerability of imipramine with that of venlafaxine. The administration of either 150 mg/day of imipramine or 225 mg/day of venlafaxine to 40 patients suffering from painful polyneuropathy improved the pain scores evaluated in the study; however, no significant differences were found between the two study drugs (6).

Table XI: Clinical studies of venlafaxine (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Pain	Randomized, double-blind, crossover	Venlafaxine, 37.5 mg po bid x 2 d Placebo	16	Venlafaxine increased the pain tolerance thereshold to electrical sural nerve stimulation and the thereshold at which pain increased, suggesting a potential analgesic effect in clinical neuropathic pain	1
Diabetic neuropathy, polyneuropathy	Open	Venlafaxine, 37.7 mg/d → up to 75 mg/d x 8 wk	13	Venlafaxine was helpful in relieving pain in diabetic patients with painful peripheral polyneuropathy, independently of mood-mediated effects	5
Polyneuropathy	Randomized, double-blind, crossover	Venlafaxine, 225 mg/d x 4 wk Imipramine, 150 mg/d x 4 wk Placebo x 4 wk	40	Venlafaxine induced some pain reduction in painful polyneuropathy, but less than imipramine	6
Breast cancer	Randomized, double-blind, crossover	Venlafaxine, 18.75 mg po od (evening) x 7 d → 37.5 mg po od (evening) → 18.75 mg po morning + 37.5 mg po eveving→ 37.5 mg po morning + 37.5 mg po evening Placebo	15	Venlafaxine alleviated maximum pain intensities of neuropthic pain but no difference compared to placebo was observed for current pain intensity or relief. Venlafaxine dosing should be carefully tailored as low doses might not be effective	7

A randomized, double-blind, placebo-controlled crossover study in 13 patients with neuropathic pain after breast cancer evaluated treatment with venlafaxine. Placebo and venlafaxine tablets (18.75 mg) were taken daily, starting with 1 tablet during week 1 and increasing by 1 tablet every week for 4 weeks. A 2-week washout period followed before patients crossed over to the other treatment. Average pain relief and maximum pain intensity were significantly reduced by venlafaxine as compared to placebo and adverse effects were similar for the two treatments (7).

1. Enggaard, T.P., Klitgaard, N.A., Gram, L.F., Arandt-Nielsen, L., Sindrup, S.H. *Specific effect of venlafaxine on single and repetitive experimental painful stimuli in humans*. Clin Pharmacol Ther 2001, 69(4): 245.

2. *Erythromelalgia: The story so far*. DailyDrugNews.com (Daily Essentials) March 14, 2002.

3. Yashar, S.S., Moiin, A. *Treatment of erythromelalgia with serotonin norepinephrine reuptake inhibitors*. 60th Annu Meet Am Acad Dermatol (Feb 22-27, New Orleans) 2002, Abst P146.

4. Sumpton, J.E., Moulin, D.E. *Treatment of neuropathic pain with venlafaxine*. Ann Pharmacother 2001, 35(5): 557.

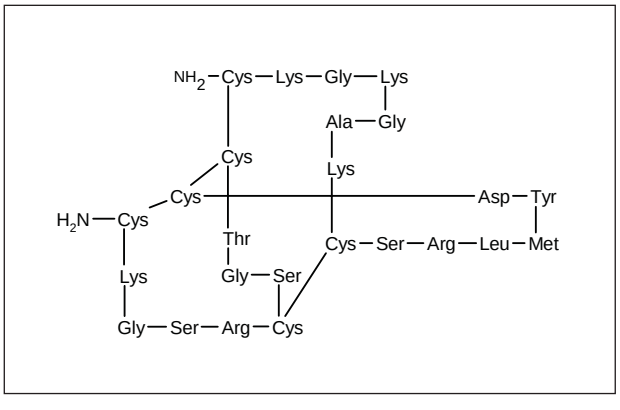
5. Perdikis, D.A., Mangiaracina, G. *Venlafaxine HCl improves painful polyneuropathy in patients with well-controlled type II diabetes mellitus*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 766.

6. Sindrup, S.H., Bach, F.W., Madsen, C., Jensen, T.S. *Venlafaxine compared to imipramine in painful polyneuropathy*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 767.

7. Tasmuth, T., Härtel, B., Kalso, E. *Venlafaxine in neuropathic pain following treatment of breast cancer*. Eur J Pain 2002, 6(1): 17.

Original monograph - Drugs Fut 1988, 13(9): 839.

Ziconotide



Elan's ziconotide (Prialt™) is an N-type calcium channel blocker with antihyperalgesic and antiallodynamic effects in animal models of chronic pain. Elan has agreed with the FDA to conduct an additional phase III study, to be initiated in the second quarter of 2002, while the FDA will allow the drug to be made available to patients for compassionate use purposes (1, 2).

The effects of long-term intrathecal ziconotide on sleep and other quality-of-life measures were determined in a multicenter, open-label trial in patients with chronic

Table XII: Clinical studies of ziconotide (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Pain-induced sleep disorder	Open, multicenter	Ziconotide, 0.1 mg/h intrathecal (titrated if needed) x 2 mo	283	Intrathecal ziconotide had a beneficial effect on quality of sleep and some parameters of daily life in patients with chronic pain	3
Pain of HIV infection and malignant neoplasm	Double-blind	Ziconotide, 0.4 μg/h (max. 21.0 μg/h) intrathecal bid x 5-6 d → 0.1-2.4 μg/h od x 5-6 Placebo	112	Intrathecal ziconotide seemed to be well tolerated and effective in the treatment of chronic pain secondary to cancer or AIDS	4
Pain of HIV infection and malignant neoplasm	Double-blind	Ziconotide Placebo	112	Ziconotide was effective in relieving chronic intractable pain of malignant origen. Its efficacy seemed to be better in cancer than in AIDS patients	5

severe pain. A total of 283 patients treated for 2 months with intrathecal ziconotide were evaluated for ambulation, sleep and the impact of pain on daily life. Ziconotide demonstrated positive effects on sleep and pain impact on daily life. The percentage of patients having 4-6 h of uninterrupted nocturnal sleep was increased from 28.3% before ziconotide to 37.4% after 2 months of drug therapy. A significant increase in sleep on ziconotide was also seen when sleep time was divided into intervals of < 4 h and > 4 h. Subjective assessment of the impact of pain on daily life showed that 37% of patients considered that pain interfered less with their daily life after treatment with ziconotide. Moreover, the percentage of patients who felt that pain dominated their life was decreased from 58.6% before ziconotide to 49.5% after 2 months of treatment with the drug (3). The results of this and the 2 studies that follow are summarized in Table XII.

A double-blind, placebo-controlled, dose-finding trial of ziconotide was conducted in 112 patients with moderate to severe chronic pain secondary to cancer or AIDS. The optimal ziconotide regimen was found to be intrathecal infusion initiated at 0.1 μg/h and increased to 0.2, 0.3, 0.6, 1.2 and 2.4 μg/h over 6 days, which was safe and produced significant analgesia in over 75% of patients (4).

Ziconotide efficacy was evaluated in a double-blind, placebo-controlled trial of patients with moderate to severe pain secondary to cancer or AIDS. The agent was found to be highly efficacious in most patients regardless of patient demographics or disease status, although cancer patients had a slightly better response than those with AIDS (5).

1. Snutch, T.P., Feng, Z.P., Doering, C. et al. *A new class of N-type calcium channel blocker efficacious in animal models of chronic pain*. Soc Neurosci Abst 2001, 27: Abst 465.1.

2. *Elan: 2001 review, 2002 projections*. DailyDrugNews.com (Daily Essentials) Feb 8, 2002.

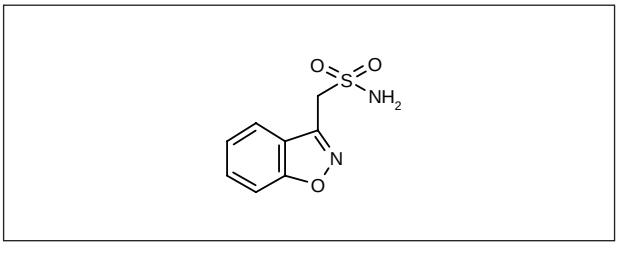
3. Royal, M., Fisher, R., Henderson, R., Drass, M., Varga, C., Ellis, D. *Effect of intrathecal ziconotide on sleep in patients with chronic, severe pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 784.

4. Leong, M.S., Webster, L.R., Ellis, D., Gaeta, R.R. *Identification of an effective and well-tolerated dose range for ziconotide, a novel non-opioid anigesic for chronic pain*. Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1617.

5. Webster, L., Gaeta, R.R., Ellis, D. *Ziconotide efficacy in patients with chronic intractable pain of malignant origin: Efficacy as a function of patients characteristics*. Proc Am Soc Clin Oncol 2001, 20(Part 1): Abst 1550.

Original monograph - Drugs Fut 1994, 19(2): 128.

Zonisamide



Zonisamide has been available in Japan from Dainippon as Excegran® for over 10 years as both monotherapy and adjunctive therapy in several types of seizures. Licensee Elan introduced zonisamide in the U.S. as Zonegran™ in 2000 as adjunctive therapy for partial seizures (1). It is currently undergoing evaluation for the treatment of migraine and neuropathic pain.

Zonisamide (10, 50 and 100 mg/kg p.o.) was evaluated in the formalin model of nociception in rats, where biphasic flinching activity was observed. Dose-dependent reductions in phase 2 flinching responses were seen with zonisamide, indicating that the agent has antihyperalgesic activity at doses which do not affect spontaneous activity, general behavior or reflexes (2).

A study tested the safety and efficacy of zonisamide, initially at 100 mg/day and increased up to 400 mg/day, in

Table XIII: Clinical studies of zonisamide (Prous Science Integriy®).

Indication	Design	Treatments	n	Conclusions	Ref.
Migraine	Open	Zonisamide, 100 mg/d → (if needed) up to 400 mg/d x 3 mo	34	Preliminary results showed that zonisamide was well tolerated and could be effective for migraine prevention, with headache severity significantly reduced	3, 4
Peripheral neuropathy	Open	Zonisamide, 100 mg (night) 1/4d x 20 d → 100 mg (night) 1/2d (titrated every 2-3 wk)	42	Zonisamide could be an alternative for treatment of refractory chronic neuropathic pain disorders	7
Peripheral neuropathy	Open, retrospective	Zonisamide, 200-300 (mean 243) mg/d	12	Preliminary results showed that zonisamide was well tolerated and effective in the treatment of neuropathic pain	8
Migraine	Open	Zonisamide, 200-300 mg/d	7	Zonisamide was well tolerated and effective in the prophylaxis of migraine	9
Diabetic nephropathy, radiculopathy	Open	Zonisamide, 100 mg/72 h x 15 d (titrated every 2 wk if needed)	25	Zonisamide could be useful in relieving pain as adjuvant therapy in refractory pain disorders	13

34 patients with refractory migraine with and without aura. Patients continued abortive medications, but not analgesics. Zonisamide treatment was associated with a significant decrease in headache severity and reductions in frequency and duration of headache, except for 9 patients who discontinued due to lack of efficacy. Side effects included paresthesias, fatigue, anxiety and weight loss, which frequently resolved on treatment, as well as agitated dysphoria and difficulty concentrating, which led to withdrawal in 2 patients each (3, 4). The results of this study and some of those that follow are summarized in Table XIII.

In an open-label trial, 33 patients with refractory migraines and mixed headache disorders were treated with zonisamide as add-on therapy to other prophylactic agents. Zonisamide was initiated at 100 mg in the evening or at bedtime every third day, which was increased to every other day and then daily up to 600 mg/day. Of 23 evaluable patients, a reduction of at least 65% in frequency of migraine and other headaches was reported by 6 patients and 8 others experienced a 25-50% reduction in symptoms; the other 9 showed no response or were noncompliant and 4 of these withdrew due to adverse events (5).

Zonisamide has been assessed for its efficacy and safety in 16 patients with refractory chronic daily headache. At doses of 100-200 mg/day for 3 months, mean number of headache days per month was reduced by 34%, average duration of headache was reduced by 24%, total headache time was reduced by 50%, mean headache rating was reduced by 23% and mean disability rating was reduced by 24%. Adverse events included mild diarrhea in 2 patients and weight loss in 9 patients (6).

Zonisamide treatment was assessed in 42 patients with chronic neuropathic pain disorders who had failed previous therapies. Treatment progressed from 100 mg every fourth night for 4 doses to every third night for 5 doses to every other night for 8 doses and to each night, after which dosing changes were made every 2-3 weeks. Zonisamide improved pain in 26 of 42 patients, with only 2 discontinuing treatment due to side effects (drowsiness) (7).

In a retrospective review of zonisamide (200-300 mg/day) in 12 outpatients with neuropathic pain, 57% of the patients rated the drug as an effective or very effective treatment. Zonisamide was well tolerated, with only 2 patients discontinuing treatment due to adverse events (8).

In an open-label study, zonisamide 200-300 mg/day was administered to 7 migraineurs with and without aura. The treatment was well tolerated and was rated as an effective or very effective prophylactic treatment by 57% of patients (9).

Two patients with complex regional pain syndrome type I were treated with zonisamide 25 mg/day. Doses were increased until week 8 or until achievement of the maximum tolerated dose, after which they were maintained for a further 2 weeks. By the end of the study, both patients had improvements on the Pain Relief Scale, in investigator global assessments and in their “worst pain”. Adverse events were mild or moderate in severity (10).

In an open-label trial, 14 of the 20 patients with neuropathic pain included in the study reported improvement in their pain symptoms following administration of 100-400 mg/day of zonisamide. The drug appeared to be more effective in a subset of patients who described their pain as “shocking” (11).

Three patients treated with zonisamide began having visual hallucinations 5 days to 4 weeks after initiation of treatment, an effect likely associated with the drug (12).

In an open-label study, patients with various chronic pain disorders (n=25) and patients with refractory migraine headaches or mixed headache disorders (n=22) were treated with zonisamide (started at 100 mg given every third day for 3-5 doses, increased to dosing every other day and then to daily doses). Zonisamide produced reductions in pain in 16 patients (13).

A method for the treatment of neuropathic pain using heteroarylmethanesulfonamides has been claimed. Particularly preferred is zonisamide. This compound was active against mechanical hyperalgesia associated with streptozotocin-induced diabetes and consequent diabetic neuropathy, as well as in the formalin test model in rats (14).

1. Tosches, W.A. *Efficacy of Zonegran monotherapy in partial seizures*. Epilepsia 2001, 42(Suppl 7): Abst 2.274.

2. McCumber, D., Chen, K.S., Meyer, K.B., Yaksh, T.L. *A study of zonisamine (Zonegran™) in the formalin model of nociception*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 715.

3. Drake, M.E., Greathouse, N.T., Armentbright, A.D., Renner, J.B. *Preventive treatment of migraine with zonisamide*. Cephalalgia 2001, 21(4): Abst P2-I15.

4. Drake, M. *Zonisamide in the prophylaxis of migraine headache*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 754.

5. Krusz, J.C. *Zonisamide in the treatment of headache disorders*. Cephalalgia 2001, 21(4): Abst P2-I16.

6. Smith, T. *Treatment of refractory chronic daily headache with zonisamide: A case series*. Cephalalgia 2001, 21(4): Abst P3-P40.

7. Krusz, J.C. *Zonisamide as a treatment for chronic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 760.

8. Cochran, J.W. *Efficacy of zonisamide in the treatment of neuropathic pain*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 752.

9. Cochran, J.W. *Efficacy of zonisamide in prophylactic treatment of migraine headaches with or without aura: Open-label experience in 7 patients*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 753.

10. Wallace, M.S. *Zonisamide for complex regional pain syndrome*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 764.

11. Patel, U., Cheville, A., Kim, P. *Zonisamide for neuropathic pain: Success with a novel adjuvant analgesic*. 21st Annu Sci Meet Am Pain Soc (March 14-17, Baltimore) 2002, Abst 762.

12. Akman, C.I., Goodkin, H.P., Rogers, D.P., Riviello, J.J. *Visual hallucinations due to zonisamide: An adverse event*. Epilepsia 2001, 42(Suppl. 7): Abst 1.164.

13. Krusz, J.C. *Zonisamide in the treatment of pain and headache disorders*. 17th World Congr Neurol (June 17-22, London) 2001, Abst P0307.

14. Benedyk, M.J. (Elan Pharmaceuticals, Inc.). *Methods for treating neuropathic pain using heteroarylmethanesulfonamides*. WO 0119321.

Original monograph - Drugs Fut 1980, 5(8): 387.