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CCC: 0377-8282/2002

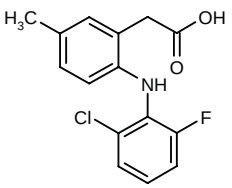
Lumiracoxib

USAN

Antiarthritic
COX-2 Inhibitor

COX-189
Prexige™

2-[2-(2-Chloro-6-fluorophenylamino)-5-methylphenyl]acetic acid



$C_{15}H_{13}ClFNO_2$

Mol wt: 293.7237

CAS: 220991-20-8

EN: 274891

Abstract

Nonsteroidal antiinflammatory drugs (NSAIDs) are the standard therapy for management of inflammation and pain. Although all available NSAIDs are ineffective against disease progression, they show similar antipyretic, antiinflammatory and analgesic effects and are particularly useful in the therapeutic management of rheumatoid arthritis and osteoarthritis. NSAIDs act by inhibiting cyclooxgenase (COX), the enzyme responsible for generation of prostaglandins that not only contribute to pain and inflammation but also are cytoprotective. Thus, because NSAIDs indiscriminately inhibit both isoforms of COX (constitutive COX-1 responsible for cytoprotective effects and inducible COX-2 responsible for inflammatory effects), they are associated with increased toxicities such as gastric mucosal erosions and ulcers and renal toxicity. The response has been the search for specific inhibitors of COX-2 which would be as effective as traditional NSAIDs in terms of pain relief but associated with fewer adverse effects. One such novel agent, lumiracoxib, has been shown to be highly selective for COX-2 with little associated gastrointestinal toxicity.

Synthesis

Lumiracoxib can be prepared by two different ways:

1) Reduction of 2-iodo-5-methylbenzoic acid (I) with BH_3/THF in THF gives 2-iodo-5-methylbenzyl alcohol (II), which is treated with refluxing 48% HBr to yield the benzyl bromide (III). Reaction of compound (III) with NaCN in EtOH/water affords the phenylacetonitrile (IV), which is hydrolyzed with NaOH in refluxing EtOH/water to provide the phenylacetic acid (V). Reaction of acid (V) with $SOCl_2$ in refluxing dichloromethane gives the corresponding acyl chloride (VI), which by reaction with dimethylamine in diethyl ether/THF yields 2-(2-iodo-5-methylphenyl)-*N*,*N*-dimethylacetamide (VII). Condensation of amide (VII) with 2-chloro-6-fluoroaniline (VIII) by means of Cu powder, Cu_2I_2 and K_2CO_3 in refluxing xylene affords 2-[2-(2-chloro-6-fluorophenylamino)-5-methylphenyl]-*N*,*N*-dimethylacetamide (IX), which is finally hydrolyzed with NaOH in refluxing butanol/water (1). Scheme 1.

2) Partial reduction of 4-methylanisole (X) with sodium in liquid ammonia/THF/EtOH gives the enol ether (XI), which is condensed with 2-chloro-6-fluoroaniline (VIII) by means of $TiCl_4$ in chlorobenzene/THF to provide imine (XII), which, without isolation, is aromatized with I_2 in AcOH/THF to yield *N*-(2-chloro-6-fluorophenyl)-*N*-(4-methylphenyl)amine (XIII). Acylation of compound (XIII) with 2-chloroacetyl chloride (XIV) at 90 °C affords the 2-chloroacetamide (XV), which is cyclized by means of $AlCl_3$ and heating at 160 °C to afford 1-(2-chloro-6-fluorophenyl)-5-methylindolin-2-one (XVI). Finally, this compound is hydrolyzed with NaOH in refluxing ethanol/water and acidified with 1N HCl (2). Scheme 2.

Alternatively, intermediate (XIII) can also be obtained by condensation of 2-chloro-*N*-(4-methylphenyl)acetamide (XVII) with 2-chloro-6-fluorophenol (XVIII) by means of K_2CO_3 in isopropanol to give 2-(2-chloro-6-fluorophenoxy)-*N*-(4-methylphenyl)acetamide (XIX), which is finally treated with MeONa in methanol to obtain *N*-(2-

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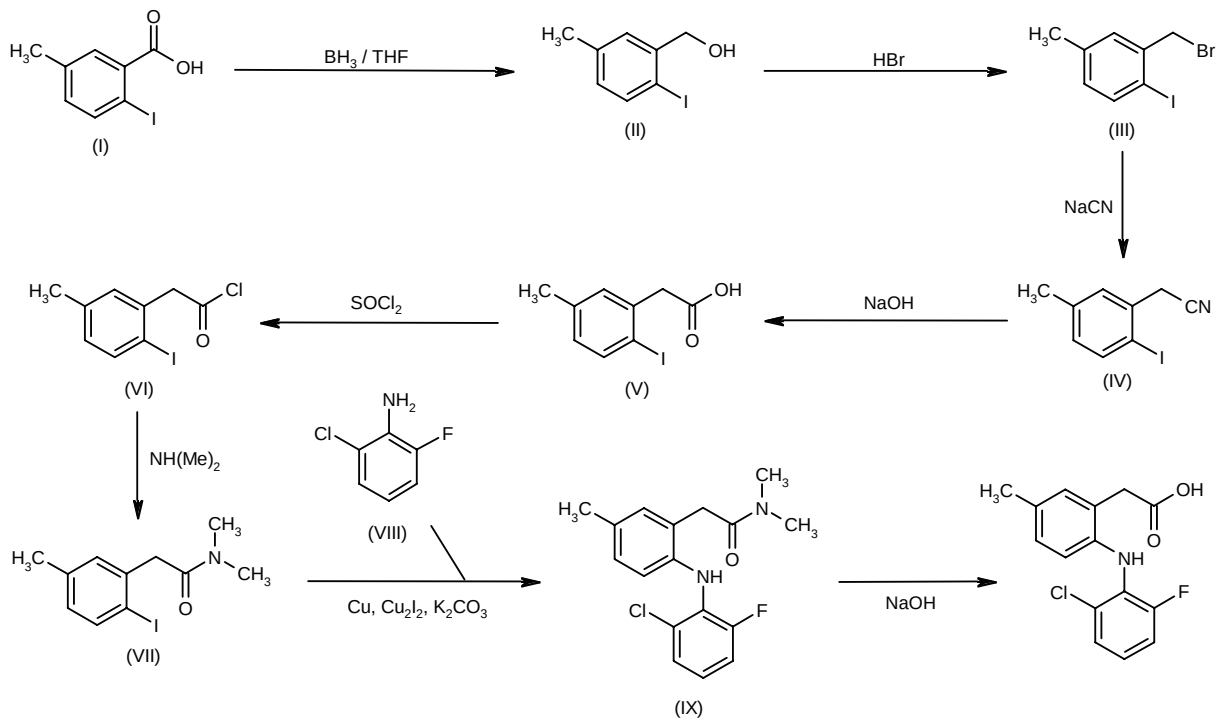
Scheme 1: Synthesis of Lumiracoxib



chloro-6-fluorophenyl)-*N*-(4-methylphenyl)amine (XIII) (2). Scheme 2.

Introduction

Extracts of plants containing salicylates have been used to treat inflammation for centuries. With the synthesis of acetylsalicylic acid (aspirin) more than 100 years ago, nonsteroidal antiinflammatory drugs (NSAIDs) became the standard therapy for management of inflammation and pain, particularly in the case of arthritis. To date, approximately 20 other NSAIDs with diverse chemical structures have reached the market. These compounds, although ineffective against disease progression, show similar antipyretic, antiinflammatory and analgesic effects. NSAIDs act via inhibition of cyclooxygenase (COX) which in turn prevents synthesis and secretion of prostaglandins, the endogenous lipid mediators that contribute to pain and inflammation but also protect gastric mucosa and maintain kidney function. As a result, these compounds display similar adverse effect profiles which include gastric mucosal erosions and ulcers, nephrotoxicity, impaired hemostasis due to platelet inhibition and aspirin-induced asthma. In the U.S. alone, as many as 16,500 patients die each year from NSAID-induced gastrointestinal complications (3-5).

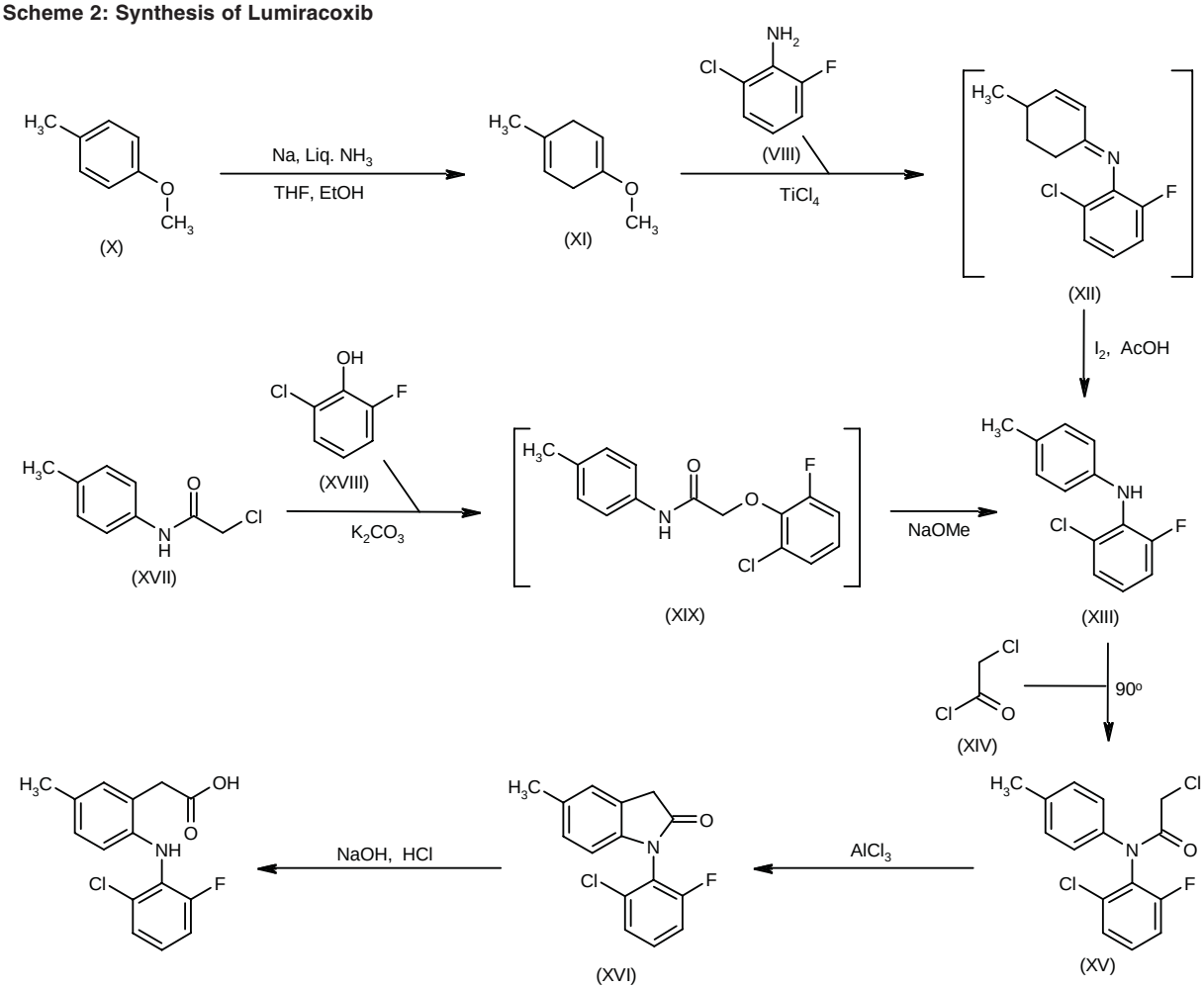
Thus, despite the therapeutic efficacy of NSAIDs, the gastrointestinal toxicities associated with these agents dictates a need for better, less toxic compounds to manage pain and inflammation. Because the cytoprotective effects and inflammatory actions of prostaglandins are mediated via 2 isoforms of the COX enzyme, constitutive COX-1 and inducible COX-2, research has focused on developing specific inhibitors of COX-2. The first COX-2 inhibitor, celecoxib (6), was launched in 1999 for the treatment of rheumatoid arthritis and osteoarthritis. Since then, the search has continued for new improved COX-2 inhibitors such as rofecoxib and etoricoxib (7, 8). Studies have demonstrated that COX-2 inhibitors are as effective but not superior to traditional NSAIDs in terms of pain relief. However, it appears that they cause significantly fewer adverse effects. Selective COX-2 inhibitors currently under development or recently launched for the treatment of pain and arthritis are shown in Table I (3, 4).

One such agent is lumiracoxib (COX-189, Prexige™) which has been shown to be highly selective for COX-2 with little associated gastrointestinal toxicity. Lumiracoxib was chosen for further development for the management of rheumatoid arthritis, osteoarthritis and pain.

Pharmacological Actions

Lumiracoxib was shown to be a potent and highly selective inhibitor of COX-2 over COX-1 in an *in vitro*

Scheme 2: Synthesis of Lumiracoxib



study. The study used a human whole blood assay which involved measurement of thromboxane B_2 (TxB_2) and LPS endotoxin-induced prostaglandin E_2 (PGE_2) levels as indicators of COX-1 and COX-2 activity, respectively. Lumiracoxib, like celecoxib and rofecoxib, was shown to more potently inhibit PGE_2 production (IC_{50} = 0.1 ± 0.04 μM) as compared to TxB_2 production (IC_{50} = 70 ± 20 μM). The COX-2 selectivity of lumiracoxib was improved 100- and 1400-fold over diclofenac and naproxen, respectively. Unlike celecoxib, rofecoxib and diclofenac which all caused 100% inhibition, lumiracoxib could not completely inhibit TxB_2 production at a high dose of 300 μM. The COX-2 selectivity ratios obtained with this assay for lumiracoxib, rofecoxib, celecoxib, diclofenac and naproxen were 700, 100, 50, 7 and 0.5, respectively (9).

Lumiracoxib also potently and dose-dependently inhibited COX-2 *ex vivo* in a study using blood from healthy male volunteers given a single lumiracoxib dose (25, 50, 100, 200, 400 or 800 mg p.o.) in the *in vitro* assay described above. Lumiracoxib dose-dependently inhibited PGE_2 production with an IC_{50} value of 0.18 μM. Moreover, while PGE_2 production was completely (100%) inhibited with lumiracoxib doses (800 mg) that achieved maximum plasma concentrations (83 μM), production of TxB_2 was unaffected (9).

The inhibitory activity and selectivity of lumiracoxib and other COX-2 inhibitors are summarized in Table II.

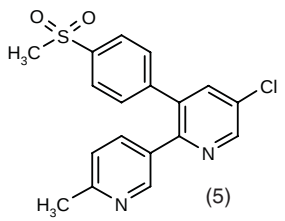
Pharmacokinetics

The pharmacokinetics of lumiracoxib have been examined in healthy volunteers in two studies and in a study involving patients with knee or hip osteoarthritis.

The first study in healthy volunteers was a randomized, double-blind, placebo-controlled, parallel-group, 6-period, time-lagged, ascending single-dose study in which 48 males were administered a single oral dose of lumiracoxib (25, 50, 100, 200, 400 and 800 mg p.o.) or placebo after an overnight fast. Pharmacodynamic analysis *ex vivo* showed that the agent at plasma levels above

Table I: COX-2 inhibitors under development or recently launched for the treatment of pain and arthritis (from Prous Science Integrity®).

Drug Name	Source	Phase
1. ABT-963*[1,2]	Abbott	I
2. CS-502*[2]	Sankyo	II
3. DRF-4848*[2]	Dr. Reddy's Res. Foundation	Preclinical
4. E-6087*[1]	Esteve	I
5. Etoricoxib[1,2]	Merck & Co.	L-2002
6. GW-406381*[1,2]	GlaxoSmithKline	I
7. Lumiracoxib[1,2]	Novartis	III
8. NNB-001*[1,2]	Nobex	Preclinical
9. NNB-004*[1,2]	Nobex	Preclinical
10. NNB-005*[1,2]	Nobex	Preclinical
11. Parecoxib Sodium[1]	Pharmacia/Yamanouchi	L-2002
12. SVT-2016*[2]	Salvat	I
13. Tilmacoxib[1,2]	Japan Tobacco	II
14. UR-8962[2]	Uriach	Preclinical
15. Valdecoxib[1,2]	Pharmacia/Pfizer/Yamanouchi	L-2002



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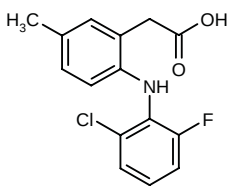

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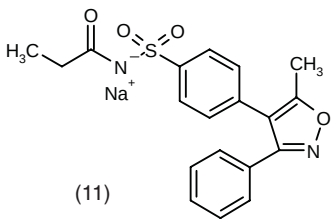

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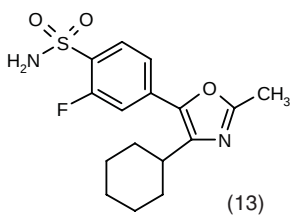

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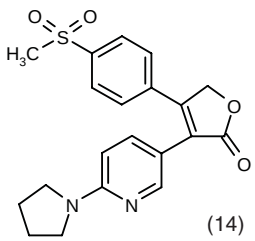

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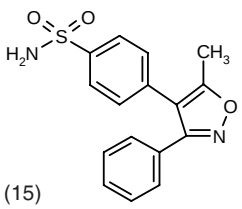

(15)

[1]Indicated for pain; [2]indicated for rheumatoid arthritis. *Structure not yet detected.

Table II: The inhibitory activity and selectivity of lumiracoxib and other COX-2 inhibitors launched or under active clinical development (from Prous Science Integrity®).

Compound	COX-1[a] IC_{50} (μM)	COX-2[a]	COX-2 selectivity COX-1/COX-2	Arthritis[c]	Edema[d] ED_{50} (mg/kg p.o.)	Pain[e]
ASA	1.7-4.5 (20, 21)	13.9->100 (20, 21)	≤ 0.22	175-185 (29, 30)	148 (29	141 (34)
Celecoxib	1.2-6.7 (9, 20, 22-24)	0.10-1.0 (9, 20, 22-24)	8.3	0.37 (22)	3.2-8.4 (22, 23, 32)	7.9 (32)
Lumiracoxib	70 (9)	0.1 (9)	700	–	–	–
Etodolac	9.0-19.6 (20, 21, 25)	2.2-3.7 (20, 21, 25)	4.8	0.5-4.0 (29-31)	23-36 (29, 31)	–
Etoricoxib	116 (26)	1.1 (26, 27)	105	0.70 (27)	0.6 (27)	0.3 (27)
Meloxicam	1.4-5.7 (20, 24, 25, 28)	0.25-2.1 (20, 24, 25, 28)	3.1	0.35 (28)	–	–
Nimesulide	4.1-10.0 (20, 21, 25)	0.18-1.9 (20, 21, 25)	9.1	–	7.0 (33)	–
Rofecoxib	18.8-63.0 (9, 20, 23, 24)	0.20-0.84 (9, 20, 23, 24)	63	–	1.5-1.7 (23, 24)	1.0 (24)
Valdecoxib	25.4 (22)	0.89 (22)	29	0.032 (22)	10.2 (22)	–

[a]Inhibition of COX-1 and COX-2 in human whole blood. [b]Selectivity for COX-2 *vs.* COX-1 calculated from mean values. [c]Inhibition of adjuvant-induced arthritis in rats. [d]Inhibition of carrageenan-induced edema in rats. [e]Inhibition of carrageenan-induced pain in the paw-pressure test in rats. ASA = acetylsalicylic acid. References in parentheses.

100 ng/ml potently inhibited blood PGE_2 while TxB_2 was unaffected, indicating COX-2 selectivity. The agent was well tolerated at all doses with no serious adverse events or discontinuations due to adverse events observed. Only 3 subjects experienced adverse events which included muscle stiffness in a patient given placebo, moderate hip discomfort thought not to be treatment-related in a patient given 200 mg lumiracoxib and mild diarrhea in a patient receiving 800 mg lumiracoxib. The C_{max} was observed between 1-4 h postdosing. Peak plasma concentrations of the agent increased in a near linear and dose-proportional manner while AUC values increased linearly and dose-proportionally over the dose range. The agent was rapidly absorbed with a t_{max} of 2-3 h, with the elimination half-life ranging from 3-6 h (10).

The pharmacokinetics of multiple-dose lumiracoxib (escalated from 50 mg b.i.d. to 100, 200 and 300 mg b.i.d. and 400 mg once daily p.o. after an overnight fast for 9 days) were examined in a randomized, double-blind, placebo-controlled trial involving 40 healthy males. The agent was well tolerated and shown to be selective for COX-2 since it had no effect on ADP/collagen-induced platelet aggregation *ex vivo*. C_{max} and AUC values increased dose-proportionately on day 1. Dose-proportionality was also seen for C_{max} and AUC at steady state but only with the twice-daily doses of 50-200 mg. The elimination half-life obtained in this study also ranged from 3-6 h and little or no accumulation was observed with multiple dosing over 9 days (11).

Dose-proportional, time-independent pharmacokinetics were reported for multiple-dose lumiracoxib in a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group study involving a total of 26 male and 26 female patients with knee or hip primary osteoarthritis (symptomatic for 3 or more months; 40 mm or greater pain intensity score on the 100 mm visual analog scale [VAS]). Patients who were receiving regular NSAIDs or other analgesics underwent a 3-7-day washout period prior to randomization to either lumiracoxib (50, 100 or 200 mg b.i.d. or 400 mg once daily p.o.), placebo or diclofenac (75 mg b.i.d. p.o.) for 4 weeks. The agent was rapidly absorbed with a median t_{max} of 2-3 h obtained. Exposure increased in a dose-proportional manner and AUC values were similar on the first and last days of dosing. Age, gender or body weight did not appear to affect exposure. Maximum reductions in VAS scores were achieved at 4-6 h postdosing on the first day and were constant on day 28. A counter-clockwise hysteresis was observed between plasma lumiracoxib concentrations and change in VAS from baseline on the first day of dosing. This suggests that the effects of the agent on pain may not be directly related to plasma concentrations but instead to distribution of the agent into another compartment such as the inflamed joint. Because similar effects on pain were observed with 400 mg once daily and 200 mg b.i.d., it was concluded that there is no influence of dosing frequency on the efficacy of lumiracoxib (12).

Clinical Studies

Results from a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study involving 60 healthy male subjects showed that lumiracoxib (200 mg b.i.d. p.o. with food for 7 days) was similar to placebo and significantly superior to naproxen (500 mg b.i.d.). Lumiracoxib was well tolerated with no changes in laboratory parameters observed. Analysis of patient serum on day 6 at 2 h postdosing showed COX-1 inhibition in naproxen-treated patients but not in those treated with lumiracoxib or placebo. Moreover, none of the lumiracoxib-treated patients developed erosions of the mucosa of the stomach and/or duodenum as compared to 13 patients in the naproxen group and 1 patient on placebo (13). The results of this study and those that follow are summarized in Table III.

A randomized, double-blind, double-dummy, placebo-controlled, 3-period, crossover study involving 25 male and female healthy volunteers further compared the effects of lumiracoxib (800 mg once daily p.o. for 8 days) with naproxen (500 mg b.i.d. p.o. for 8 days). *Ex vivo* analysis of whole blood showed that naproxen significantly reduced both platelet TxB_2 (*i.e.*, COX-1) concentrations as compared to placebo; lumiracoxib also slightly reduced platelet TxB_2 as compared to placebo although this effect was concluded not to be clinically significant. Both naproxen and lumiracoxib significantly inhibited LPS-induced PGE_2 production (*i.e.*, COX-2) as compared to placebo. Results from this study also showed that naproxen, unlike lumiracoxib, significantly increased the percentage of administered $^{51}Cr\text{-}EDT_A$ recovered in urine in a 0-5-h period indicating increased intestinal permeability as compared to lumiracoxib and placebo (1.215% *vs.* 0.739% and 0.601%, respectively). No gastric ulcers were detected in any of the treatment groups (14).

The safety, tolerability and efficacy of lumiracoxib (200 or 400 mg once daily for 13 weeks) were shown and compared to ibuprofen (800 mg t.i.d.) and celecoxib (200 mg once daily) in a multicenter, double-blind, parallel-group study involving 1042 patients with osteoarthritis. Of the 1011 evaluable patients, significantly lower cumulative gastroduodenal ulcer rates were obtained for patients treated with lumiracoxib (4.3 and 4% for the respective doses) and celecoxib (3.2%) as compared to ibuprofen (15.7%). A higher rate of gastrointestinal disorders was seen in the ibuprofen group (55.4%) as compared to lumiracoxib and celecoxib (46.5-50.4%), particularly upper abdominal pain (28.8% for ibuprofen *vs.* 16.7, 23.1 and 15.9% for lumiracoxib 200 mg, 400 mg and celecoxib, respectively). In addition, more patients discontinued due to adverse events (mainly gastrointestinal events) in the ibuprofen group (12.7%) as compared to lumiracoxib (6.8 and 5%, respectively) and celecoxib (5.8%) and more ibuprofen-treated patients (1.6%) suffered serious gastrointestinal adverse events as compared to the other groups (0.4, 0.4 and 0.8% for lumiracoxib 200 mg, 400 mg and celecoxib, respectively). One patient administered 200 mg lumiracoxib required hospitalization for a

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, multicenter	Lumiracoxib, 200 mg p.o. b.i.d. x 7 d (n=20) Naproxen, 500 mg p.o. b.i.d. x 7 d (n=20) Placebo (n=20)	60	Compared with naproxen, lumiracoxib had a favorable, placebo-like gastrointestinal tolerability profile in terms of gastric and duodenal erosions in healthy volunteers	13
Healthy volunteers	Randomized, double-blind, crossover	Lumiracoxib, 800 mg p.o. o.d. x 9 d Naproxen, 500 mg p.o. b.i.d. x 9 d Placebo	25	Lumiracoxib was well tolerated and demonstrated highly selective and potent COX-2 inhibitory activity while sparing gastric mucosal prostaglandin production	14
Osteoarthritis	Randomized, double-blind, multicenter	Lumiracoxib, 200 mg p.o. o.d. x 13 wk (n=264) Lumiracoxib, 400 mg p.o. o.d. x 13 wk (n=260) Celecoxib, 200 mg p.o. o.d. x 13 wk (n=258) Ibuprofen, 800 mg p.o. t.i.d. x 13 wk (n=260)	1042	Lumiracoxib showed a safety and gastrointestinal tolerability profile superior to that of ibuprofen and similar to that of celecoxib, with a lower incidence of gastroduodenal ulcers compared to ibuprofen	15
Osteoarthritis	Randomized, double-blind, multicenter	Lumiracoxib, 50 mg p.o. b.i.d. x 4 wk (n=98) Lumiracoxib, 100 mg p.o. b.i.d. x 4 wk (n=96) Lumiracoxib, 200 mg p.o. b.i.d. x 4 wk (n=99) Lumiracoxib, 400 mg p.o. o.d. x 4 wk (n=99) Diclofenac, 75 mg p.o. b.i.d. x 4 wk (n=94) Placebo (n=97)	583	Lumiracoxib was well tolerated and highly effective in reducing pain and showed a better tolerability profile than diclofenac in patients with osteoarthritis of the knee or hip	16, 17
Dental pain	Randomized, double-blind	Lumiracoxib, 100 mg (n=51) Lumiracoxib, 400 mg (n=50) Ibuprofen, 400 mg (n=51) Placebo (n=50)	202	Lumiracoxib was well tolerated and effective in relieving dental pain at doses of 400 mg, and demonstrated a rapid onset and prolonged duration of analgesia in patients after the extraction of 2 or more impacted third molars	18

serious adverse event of mild upper abdominal pain and another administered 400 mg lumiracoxib, discontinued for severe abdominal pain. Two patients in the celecoxib group suffered serious adverse events of severe rectal bleeding and moderate gastric ulcer pain, respectively. Serious gastrointestinal adverse events seen in the ibuprofen groups were moderate worsening of inguinal hernia, mild duodenal ulcer hemorrhage, moderate pyloric ulcer and severe gastric ulcer (15).

The efficacy and safety of lumiracoxib (50, 100, 200 mg b.i.d. or 400 mg once daily for 4 weeks) were demonstrated and compared to diclofenac (75 mg b.i.d. for 4 weeks) in a multicenter, randomized, placebo-controlled trial involving 583 patients with osteoarthritis (VAS of at least 40 mm over the last 24 h) washed out of previous NSAID therapy (for 3-7 days). Lumiracoxib treatment resulted in a tolerability profile that was superior to diclofenac and comparable to placebo. No serious adverse events were reported in any of the groups receiving lumiracoxib and incidence of peripheral edema was similar in all treatment groups. The minimum effective detectable regimen was the 50 mg lumiracoxib group. The percent of responders (*i.e.*, 20% reduction in overall pain intensity according to changes in VAS scores from baseline) for the lumiracoxib groups were 68.8, 67.4, 69.8 and 73.5%, respectively, as compared to 75.3% in the diclofenac groups and 53.1% in placebo. The estimated odds ratios (*i.e.*, >1 = better odds of responses in active treatment group) for the lumiracoxib groups with respect to placebo at week 4 were 2.12, 2.06, 2.25 and 2.73 for the lumiracoxib 50 mg, 100 mg and 200 mg b.i.d. and 400 mg once-daily groups, respectively; the odds ratio for the diclofenac group with respect to placebo was 2.96. The estimated odds ratios of the lumiracoxib groups with respect to diclofenac were 0.72, 0.70, 0.76 and 0.72, respectively; the odds ratio for placebo with respect to diclofenac was 0.34. These results demonstrate that 400 mg once-daily lumiracoxib was more effective than the lumiracoxib twice-daily regimens and comparable to diclofenac in producing a 20% reduction in osteoarthritis pain intensity scores from baseline (16, 17).

Lumiracoxib (100 or 400 mg single dose) was also found to be effective in managing postoperative dental pain when compared to ibuprofen (400 mg) in a randomized, double-blind, parallel study involving 2020 men and women with moderate to severe pain following extraction of 2 or more impacted third molars. Both doses of lumiracoxib were well tolerated and together with the ibuprofen group were significantly superior to placebo. The 400 mg lumiracoxib regimen was as effective as ibuprofen in terms of the median times to onset of analgesia (53, 38 and 42 min for lumiracoxib 100 mg, 400 mg and ibuprofen, respectively, *vs.* > 12 h for placebo) but was significantly superior to ibuprofen (> 12 h *vs.* 8 h 1 min), 100 mg

lumiracoxib (7 h) and placebo (1 h 59 min) in increasing the median time to rescue medication use. Thus, a single 400 mg lumiracoxib dose resulted in rapid analgesia onset for a prolonged period of time (18).

Lumiracoxib continues to undergo phase III development. The TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial) has recently been initiated to examine the safety, efficacy and tolerability of lumiracoxib as a treatment for symptoms of arthritis and pain as compared to ibuprofen and naproxen. More than 18,000 patients including those over the age of 50 suffering from osteoarthritis, will be enrolled in several U.S. sites. The primary and secondary endpoints of the trial are gastrointestinal and cardiovascular safety, respectively (19).

Source

Novartis AG (CH).

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