Lumiracoxib, an inhibitor of cyclooxygenase 2 (COX-2), is under development by Novartis for the potential treatment of osteoarthritis, rheumatoid arthritis and pain. By late December 2000, phase III trials had been initiated and were ongoing in December 2001.

**Introduction**
Following the discovery of the inducible isoform of cyclooxygenase (COX)-2, the expectation emerged that the development of new agents that selectively inhibit COX-2 would optimize the analgesic and anti-inflammatory properties of non-steroidal anti-inflammatory drugs (NSAIDs), while minimizing the potential for gastrointestinal (GI) adverse events (mediated by inhibition of COX-1). It is now appreciated that COX-2 is also expressed in a variety of non-inflammatory tissues, including kidney, brain, neoplasms, bone and cartilage, particularly under 'physiological stress' conditions. In the kidney, COX-2-derived prostaglandins help modulate vascular tone in addition to salt and water homeostasis. It is, therefore, not surprising that clinical studies indicate that selective COX-2 inhibitors, like conventional NSAIDs, cause comparable rates of edema and hypertension and may impair renal function in the setting of congestive heart failure or volume depletion [468857].

To date, only two selective COX-2 inhibitors have been successfully launched. Celecoxib (celebrex) is approved for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA), and for the management of pain indications, such as pain associated with cancer and dysmenorrhea. The approved indications for rofecoxib (Vioxx) are treatment of OA, acute pain and dysmenorrhea. Usage of these COX-2 inhibitors increased rapidly until a study was published in the August 2001 issue of *Journal of the American Medical Association*. The authors re-analyzed data from pivotal clinical trials and found that both rofecoxib and celecoxib might have cardiac side effects [451465].

**Synthesis and SAR**
The synthesis of lumiracoxib involves the coupling of N,N-dimethyl-5-methyl-2-iodophenylacetamide with 2-chloro-6-fluoroaniline in the presence of copper powder, copper(I) iodide and anhydrous potassium carbonate, and refluxing the mixture in xylenes for 48 h. Work-up led to the isolation of lumiracoxib, which was characterized by melting point (158 to 159°C) [WO-09911605].

Four claimed routes for the process preparation of lumiracoxib are reported in WO-00123346. For example, 4-bromotoluene and 2-chloro-6-fluoroaniline are coupled in the presence of palladium catalyst under Buchwald chemistry conditions. The resulting diphenylamine undergoes N-acylation with chloroacetyl chloride before cyclization to the corresponding lactam under Friedel-Crafts alkylation conditions. Lumiracoxib is finally liberated by hydrolysis.

A formulation, comprising lumiracoxib (200 mg), microcrystalline cellulose (103.4 mg), lactose (46.6 mg), povidone (16 mg), titanium dioxide (16 mg), croscarmellose sodium (16 mg) and magnesium stearate (2 mg), is specifically claimed in WO-09911605.

**Pharmacology**
Studies performed *in vitro* revealed that the COX-2 selectivity of lumiracoxib was 100- and 1400-fold higher than that of the COX inhibitors diclofenac and naproxen, respectively. In primary human fibroblasts induced with...
IL-1 to synthesize COX-2 and HEK293 cells stably transfected to constitutively express COX-1, the lumiracoxib prodrug, 5-alkyl-2-arylamino phenylacetic acid, had an IC50 value of 0.007 µM against COX-2 with no activity against COX-1 at 30 µM. This compound showed an ED₅₀ value in the range of 0.2 to 0.6 mg/kg po in the rat air pouch model for measuring inhibition of PGE₂ formation [WO-09911605].

The in vivo inhibition of thromboxane B₂ was investigated in serum from fasted rats that had been administered lumiracoxib (800 mg) or placebo 30 min prior to sacrifice. No significant inhibition was observed compared to placebo, and the ED₅₀ value was 50- to 100-fold greater than for COX-2 inhibition [411639], [WO-09911605].

In the Randall-Selitto paw pressure assay of antinociception in Wistar rats, lumiracoxib increased the pain threshold in an inflamed paw at 10 mg/kg po. This was selective with no threshold elevation in the non-inflamed paw [WO-09911605].

Metabolism
Lumiracoxib shows no accumulation in plasma, does not interact with antacids and has no effect on platelet aggregation at 2- to 4-fold the therapeutic dose [468743]. It has a unique pharmacokinetic profile; it is an acid, and has a high protein-binding capacity (99.9%) and a t₁/₂ of 3 to 6 h, but can still be applied once-daily [468743], [WO-00220090].

OA patients were administered doses of 50, 100 and 200 mg tid or 400 mg/day, and the changes in AUC and Cₘₐₓ were measured on day 28. This produced Tₘᵰ values of 2 to 3 h, with Cₘᵰ values of 4378 and 4788 ng/ml at the 200 mg bid and 400 mg/day doses, respectively; AUC values were dose proportional and were similar on days 0 and 28, suggesting that lumiracoxib rapidly reaches steady state in plasma [WO-00220090].

Toxicity
The lumiracoxib prodrug is free of gastric ulcerogenic effects (at 100 mg/kg po) and has only minimal effects on intestinal permeability (at 30 mg/kg po) in rats [WO-09911605].

Clinical Development
Phase I
Phase I trials showed that lumiracoxib was well tolerated at up to 800 mg and that there were no serious adverse effects or clinically significant laboratory abnormalities [342937]. In one trial, 60 healthy male volunteers received either 200 mg bid of lumiracoxib, 500 mg bid of naproxen or placebo for 7 days. The presence of gastric or duodenal erosions was determined by endoscopy before dosing began and again following 7 days of dosing. Erosions were detected in 13 of 20 subjects in the naproxen group and 1 of 20 in the placebo group, whereas no erosions were observed in the lumiracoxib group. In another trial of 25 healthy volunteers, lumiracoxib (800 mg/day), naproxen (500 mg/day) or placebo were administered for 8 days. Ulcers or erosions were detected in 75% of the naproxen group and 12% of the placebo group, although none were detected in the lumiracoxib group [451313], [451315], [451430], [451715], [451842].

In vivo studies confirmed the COX-2 selectivity of lumiracoxib; in healthy volunteers treated for 8 days, it inhibited lipopolysaccharide (LPS)-induced PGE₂ synthesis in whole blood more effectively than naproxen, with mean PGE₂ concentrations of 20654 and 4729 pg/ml for naproxen (500 mg bid), placebo and lumiracoxib (800 mg/day), respectively. It had no significant effect on gastric mucosal PGE₂ expression (mean gastric mucosal PGE₂ concentrations = 68, 221 and 156 pg/mg for the naproxen, placebo and lumiracoxib groups, respectively) [451842].

Phase II
Phase II trials in OA, RA and pain were initiated in September 1999 [342937]. In a placebo-controlled, 150-patient phase II study in dental pain, lumiracoxib (400 mg single dose) demonstrated a potent analgesic effect [411639]. A double-blind, randomized, parallel-group study involving subjects with moderate-to-severe pain following extraction of two or more impacted third molars (n = 202), found that treatment with lumiracoxib (400 mg single dose) resulted in rapid and prolonged pain relief and was equivalent to ibuprofen and superior to placebo in analgesic onset (38 min versus 42 min and > 12 h, respectively) and superior in median time to rescue medication (> 12 h versus 8 h and 2 h, respectively) [448856]. Clinical results from placebo-controlled phase II trials in OA (400 mg/day; n = 94 to 99 patients per arm) and RA (200 mg bid; n = 87 to 99 patients per arm) demonstrated that lumiracoxib performs better than placebo for OA and RA and is comparable to diclofenac (75 mg bid) for RA [411639].

A multinational, dose-ranging trial evaluated the efficacy of lumiracoxib in patients with OA of the hip and knee (n = 583). Patients were treated for 4 weeks with lumiracoxib (400 mg/day, 50, 100 or 200 mg bid); diclofenac (75 mg bid); or placebo. The minimum effective dose of lumiracoxib was 50 mg bid. All regimens of lumiracoxib were comparable to diclofenac and superior to placebo in mean improvements in visual analog scale (VAS) pain, WOMAC index, HAQ index and global assessments [468864]. The assessment of the responder rate of lumiracoxib in OA pain showed that lumiracoxib at 400 mg/day is highly effective for the treatment of patients with OA. The findings suggested that lumiracoxib provides the same strong efficacy as high doses of diclofenac (75 mg bid) in treatment response defined as a 20% reduction in OA pain intensity based on VAS measure [454848].

A multicenter, double-blind study investigated upper GI safety and tolerability in 1042 OA patients who were randomized to one of four treatment groups: 200 or 400 mg/day of lumiracoxib (n = 264 and 260, respectively); 800 mg/day of lumiracoxib, 5-alkyl-2-arylamino phenylacetic acid, had an IC₅₀ value of 0.007 µM against COX-2 with no activity against COX-1 at 30 µM. This compound showed an ED₅₀ value in the range of 0.2 to 0.6 mg/kg po in the rat air pouch model for measuring inhibition of PGE₂ formation [WO-09911605].
mg tid of ibuprofen (n = 258); or 200 mg/day of celecoxib (n = 260). Patients were evaluated by endoscopy for cumulative incidence of GI ulcers (diameter > 3 mm) at baseline, week 4 and week 13. Frequency of adverse events, including GI serious adverse events, was also recorded. At both doses, lumiracoxib demonstrated a superior GI safety and tolerability profile compared with ibuprofen. With respect to the occurrence of gastroduodenal ulcers, lumiracoxib was statistically superior to ibuprofen (p < 0.01). The study showed that 15.7% of patients in the ibuprofen group experienced ulcers compared with 4.3 and 4.0% in the lumiracoxib groups (200 and 400 mg/day, respectively), which was comparable to the celecoxib group (3.2%) [454848], [468909], [468911].

Phase III
A multinational, double-blind, randomized, active-controlled, parallel-group worldwide study (TARGET) has been initiated. More than 18,000 patients with OA (50 years and older) are to receive one year of treatment with either lumiracoxib (400 mg/day), ibuprofen (800 mg tid) or naproxen (500 mg bid). The primary safety endpoints include perforation, obstructions and bleeding, while the secondary endpoints include cardiovascular events, combined cardiovascular and gastrointestinal events and safety [427419], [440183], [451842], [451913]. As of July 2002, interim results of the TARGET study were expected to be available in 2003, with final results anticipated for mid-2004 [455859], [458765].

Side Effects and Contraindications
There have been no serious adverse events reported from the limited number of clinical studies on lumiracoxib [451842]. Of patients treated with lumiracoxib (200 and 400 mg/day), 4.3 and 4.0% experienced GI ulcers following 13 weeks of treatment, which was comparable to the celecoxib group (3.2%) and lower than the ibuprofen group (15.7%) [454848]. Of patients in the lumiracoxib groups, 16.7 and 23.1% experienced upper abdominal pain after 13 weeks of treatment (200 and 400 mg/day, respectively) [468909], [468911]. Lumiracoxib demonstrates liver and renal safety comparable to the other COX-2 inhibitors [468743].

Patent Commentary
Novel 5-alkyl-2-arylaminoacetic acids with selective inhibitory properties against COX-2 are claimed by Novartis in WO-09911605, which was published in March 1999 and will expire in August 2017. In April 2001, Novartis claimed a process for preparing 2-phenylamino-5-alkylphenyl acetic acids, which are stated to be selective COX-2 inhibitors, comprising cleavage of a novel cyclic lactam intermediate with a base in WO-00123346. Formulations of lumiracoxib, suitable for once-daily administration, were claimed by Novartis in March 2002, in WO-00022290, due to expire in September 2020.

Current Opinion
Clinical studies have demonstrated that lumiracoxib is effective in the treatment of dental pain, OA and RA, and is comparable to the conventional NSAIDs diclofenac and ibuprofen. Lumiracoxib is well tolerated and its GI safety profile is superior to conventional NSAIDs. So far, no claim can be made that this drug is more effective, better tolerated or more useful than currently available COX-2 inhibitors. Novartis is conducting a clinical trial that will directly compare lumiracoxib to the current market leaders to investigate GI and cardiovascular side effects, hoping to demonstrate that its product has a safety advantage. If this proves to be the case, lumiracoxib may capture a substantial portion of the considerable market for COX-2 inhibitors. The theoretical rationale for this advantage is, however, weak at present.

As with other conventional NSAIDs, there are no data showing the effects of lumiracoxib on underlying joint health in the treatment of OA and RA [468870]. As COX-2 is found in cartilage, it is necessary to elucidate the role of all COX-2 inhibitors, including lumiracoxib, on disease progression of arthritis using biochemical markers of cartilage damage and/or novel imaging approaches, such as magnetic resonance imaging.

Commercial Opinion

Development history
By September 1999, the company had expected to make regulatory submissions in the fourth quarter of 2002 and to launch lumiracoxib in late 2003 [342937], [458765]; in October 2002, Novartis revealed that US and EU filings were on track for December 2002 with launches forecast in 2004 [467193]. In Japan, lumiracoxib was listed as beyond phase II trials for OA, RA and pain in October 2002 [466916]. In November 2001, it was reported that Novartis planned to look for a commercialization partner for the compound [430088].
### Literature classifications

Key references relating to the drug are classified according to a set of standard headings to provide a quick guide to the bibliography. These headings are as follows:

**Clinical:** Reports of clinical phase studies in volunteers providing, where available, data on the following: whether the experiment is placebo-controlled or double- or single-blind; number of patients; dosage.

<table>
<thead>
<tr>
<th>Effect Studied</th>
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<th>Result</th>
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<tr>
<td>Efficacy in inhibition of COX-2.</td>
<td>LPS-induced PGE₂ synthesis in whole blood. Phase I trial in healthy volunteers (n = 25) treated with lumiracoxib (800 mg/day) for 8 days.</td>
<td>Lumiracoxib inhibited PGE₂ synthesis.</td>
<td>451842</td>
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<td>Efficacy in inhibition of COX-1.</td>
<td>Gastric mucosal PGE expression and blood platelet thromboxane B₂ concentrations. Phase I trial in healthy volunteers (n = 25) treated with lumiracoxib (800 mg/day) for 8 days.</td>
<td>Lumiracoxib had no effect on PGE₂ and thromboxane B₂ production.</td>
<td>451842</td>
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<tr>
<td>GI safety and tolerability</td>
<td>A multicenter, double-blind phase II study in OA patients (n = 1042) randomized to one of four treatment groups: lumiracoxib (200 or 400 mg/day), ibuprofen (800 mg tid) or celecoxib (200 mg/day).</td>
<td>Both doses of lumiracoxib demonstrated a superior GI safety and tolerability profile compared with ibuprofen.</td>
<td>454848, 468911</td>
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<tr>
<td>Symptomatic relief of OA.</td>
<td>A dose-ranging phase II trial evaluating the efficacy of lumiracoxib in patients with OA of the hip and knee (n = 583). Patients were treated for 4 weeks with lumiracoxib (400 mg/day) or 50, 100 or 200 mg bid), diclofenac (75 mg bid) or placebo.</td>
<td>All regimens of lumiracoxib were comparable to diclofenac and superior to placebo in mean improvements in VAS pain, WOMAC index, HAQ index and global assessments.</td>
<td>454848, 468864</td>
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<td>Symptomatic relief of OA.</td>
<td>Placebo-controlled phase II trials in RA patients (n = 87 to 99 per arm) treated with lumiracoxib (200 mg bid).</td>
<td>Lumiracoxib is comparable to diclofenac in VAS pain over 24 h.</td>
<td>411639</td>
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<td>Safety and tolerability.</td>
<td>Phase I trial in healthy volunteers (n = 60) treated with lumiracoxib (200 mg bid) or naproxen (500 mg bid).</td>
<td>Duodenal erosions were detected in 13 of 20 subjects in the naproxen group, whereas no erosions were observed in the lumiracoxib group.</td>
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<td>Safety and tolerability.</td>
<td>Phase I trial in healthy volunteers (n = 25) treated with lumiracoxib (800 mg/day) or naproxen (500 mg bid).</td>
<td>Ulcers or duodenal erosions were detected in 75% of the naproxen group and 12% of the placebo group; none were detected in the lumiracoxib group.</td>
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<td>Pain relief.</td>
<td>Phase II trial involving subjects with dental pain (n = 202) treated with lumiracoxib (400 mg single dose).</td>
<td>Lumiracoxib resulted in rapid and prolonged pain relief and was superior to ibuprofen and placebo in analgesic onset.</td>
<td>448856</td>
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<tr>
<td>Symptomatic relief of OA.</td>
<td>Placebo-controlled phase II trials in OA patients (94 to 99 per arm) treated with lumiracoxib (400 mg/day).</td>
<td>Lumiracoxib shows significantly greater pain relief compared to placebo.</td>
<td>411639</td>
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### Associated references

**Associated patent**

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**Associated references**

- **of outstanding interest**
- **of special interest**

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