Lumiracoxib Novartis

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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.

Originator Novartis AG

Status Phase III Clinical

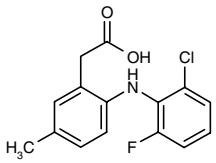
Indications Osteoarthritis, Pain, Rheumatoid arthritis

Actions Analgesic, Cyclooxygenase 2 inhibitor, Non-steroidal anti-inflammatory

Biotechnology Enzyme inhibitor

Synonyms COX-189, COX-189A, Prexige

CAS Benzeneacetic acid, 2-[(2-chloro-6-fluorophenyl)-amino]-5-methyl-
Registry No: 220991-20-8



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 America Medical Association*. The authors re-analyzed data from pivotal clinical trials and found that both rofecoxib and celecoxib might have cardiac side effects [451465]. Subsequent meta-analyses failed to confirm this finding, however, and the adverse cardiac effect has been limited to one rofecoxib trial (VIoxx Gastrointestinal Outcomes Research; VIGOR) in RA [451465].

Lumiracoxib is a second-generation COX-2 inhibitor developed by Novartis for the potential treatment of OA, RA and pain [342937]. It is currently in the phase III TARGET (Therapeutic lumiracoxib Arthritis Research and GI Event Trial) trial, which will examine, as a primary objective, the GI safety of lumiracoxib compared with NSAIDs, in addition to cardiovascular safety as a specified secondary endpoint [451913].

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-00220090.

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-arylaminophenylacetic acid, had an IC_{50} value of 0.007 μM against COX-2 with no activity against COX-1 at 30 μM. This compound showed an ED_{50} value in the range of 0.2 to 0.6 mg/kg po in the rat air pouch model for measuring inhibition of PGE_2 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 ED_{50} value was 50- to 100-fold greater than for COX-2 inhibition [411639], [WO-09911605].

In the Randall-Selitto paw pressure assay of anti-nociception 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 $t_{1/2}$ 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 C_{max} were measured on day 28. This produced T_{max} values of 2 to 3 h, with C_{max} 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 bid) 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 PGE_2 synthesis in whole blood more effectively than naproxen, with mean PGE_2 concentrations of 7054, 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 PGE_2 expression (mean gastric mucosal PGE_2 concentrations = 68, 221 and 156 pg/mg for the naproxen, placebo and lumiracoxib groups, respectively) and blood platelet thromboxane B2 concentrations (mean platelet thromboxane B2 concentrations = 10, 397 and 302 ng/ml for the naproxen, placebo and lumiracoxib groups, respectively) [451842]. Another trial in healthy volunteers (n = 6) also revealed that mean serum concentration of thromboxane B2 in the naproxen group (500 mg bid) was less than 5% of the mean placebo group value, whereas mean concentration for the lumiracoxib group (200 mg bid) was similar to placebo after 6 days of treatment [451842]. These results suggest that lumiracoxib has minimal effects on the COX-1 isoform.

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 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 lurimacoxib groups, 16.7 and 23.1% experienced upper abdominal pain after 13 weeks 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-arylaminophenylacetic 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

In July 2000, Vontobel predicted sales of SFr 100 million in 2003, rising to SFr 1 billion in 2004 [378871]. In November 2000, Lehman Brothers estimated launch in 2003, with worldwide peak sales of US $750 million in 2011 [392075]. In December 2000, and later in February 2001, Merrill Lynch predicted sales of SFr 100 million in 2003 and SFr 261 million in 2005 [394812], [411704]. In August 2001, Deutsche Bank estimated sales of SFr 75 million in 2003, rising to SFr 700 million in 2005 [422674].

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].

Developer	Country	Status	Indication	Date	Reference
Novartis AG	Switzerland	Phase III	Pain	11-DEC-00	392881
Novartis AG	Switzerland	Phase III	Rheumatoid arthritis	11-DEC-00	392881
Novartis AG	Switzerland	Phase III	Osteoarthritis	11-DEC-00	392881
Novartis AG	Japan	Clinical	Rheumatoid arthritis	14-OCT-02	466916
Novartis AG	Japan	Clinical	Osteoarthritis	14-OCT-02	466916
Novartis AG	Japan	Clinical	Pain	14-OCT-02	466916

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.

Clinical

Effect Studied	Model Used	Result	Reference
Efficacy in inhibition of COX-2.	LPS-induced PGE_2 synthesis in whole blood. Phase I trial in healthy volunteers (n = 25) treated with lumiracoxib (800 mg/day) for 8 days.	Lumiracoxib inhibited PGE_2 synthesis.	451842
Efficacy in inhibition of COX-1.	Gastric mucosal PGE_2 expression and blood platelet thromboxane B2 concentrations. Phase I trial in healthy volunteers (n = 25) treated with lumiracoxib (800 mg/day) for 8 days.	Lumiracoxib had no effect on PGE_2 and thromboxane B2 production.	451842
GI safety and tolerability	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).	Both doses of lumiracoxib demonstrated a superior GI safety and tolerability profile compared with ibuprofen.	454848 468911
Symptomatic relief of OA.	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.	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.	454848 468864
Symptomatic relief of RA.	Placebo-controlled phase II trials in RA patients (n = 87 to 99 per arm) treated with lumiracoxib (200 mg bid).	Lumiracoxib is comparable to diclofenac in VAS pain over 24 h.	411639
Safety and tolerability.	Phase I trial in healthy volunteers (n = 60) treated with lumiracoxib (200 mg bid) or naproxen (500 mg bid).	Duodenal erosions were detected in 13 of 20 subjects in the naproxen group, whereas no erosions were observed in the lumiracoxib group.	451842
Safety and tolerability.	Phase I trial in healthy volunteers (n = 25) treated with lumiracoxib (800 mg/day) or naproxen (500 mg bid).	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.	451842
Pain relief.	Phase II trial involving subjects with dental pain (n = 202) treated with lumiracoxib (400 mg single dose).	Lumiracoxib resulted in rapid and prolonged pain relief and was superior to ibuprofen and placebo in analgesic onset.	448856
Symptomatic relief of OA.	Placebo-controlled phase II trials in OA patients (94 to 99 per arm) treated with lumiracoxib (400 mg/day).	Lumiracoxib shows significantly greater pain relief compared to placebo.	411639

Associated patent

Title Certain 5-alkyl-2-arylaminophenylacetic acids and derivatives.

Assignee Novartis AG

Publication WO-09911605 11-MAR-99

Priority US-00069837 28-AUG-97

Inventors Fujimoto RA, McQuire LW, Mugrage BB, Van Duzer JH, Xu D.

Associated references

•• of outstanding interest
• of special interest

342937 **Novartis R&D Investor Seminar, New York.** Novartis AG *COMPANY WORLD WIDE WEB SITE* 1999 September 21

378871 **Analyst Report: Novartis (Switzerland/Pharma).** Bank Vontobel AG *BANK VONTOBEL* 2000 July

392075 **Pharmaceuticals Europe (Novartis).** *LEHMAN BROTHERS INC* 2000 November 30

392881 **Novartis R&D Investor Seminar, Basel.** Novartis AG *COMPANY WORLD WIDE WEB SITE* 2000 December 06

394812 **Novartis.** *MERRILL LYNCH CAPITAL MARKETS* 2000 December 18

411639 **Investor relations: Presentations - EXANE Pharma Seminar, Paris.** Novartis AG *COMPANY PRESENTATION* 2001 May 10

411704 **Novartis: Best foot forward.** Barnes N *MERRILL LYNCH CAPITAL MARKETS* 2001 February 19

422674 **Novartis: Encouraging mix and momentum in H1.** *DEUTSCHE BANC ALEX BROWN* 2001 August 16

427419 **Novartis R&D Day October 30, 2001.** Novartis AG *COMPANY PRESENTATION* 2001 October 30

430088 **Novartis COX-189 TARGET study will assess CV safety of COX-2 inhibitor.** *FDC REPORTS PINK SHEET* 2001 **63** 46 32

440183 **Novartis Annual Report 2001: Advance copy.** Novartis AG *ANNUAL REPORT* 2002 February 14

448856 **Temporal aspects of COX189 efficacy in acute dental pain.** Manning DC, Fricke J, Zelenakas K, Jayawardene S *CLIN PHARMACOL THER* 2002 **71** 2 Abs MPI-47

451313 **No acute gastroduodenal erosive injury in a study of COX-189, a new highly selective COX-2 inhibitor.** Atherton C, Hayer R, Stevenson D, Jones JEW, McKaig B, Cunliffe R, Bebb J, Bonner J, Scott G, Rodorf C, Hawkey C *GASTROENTEROLOGY* 2002 **122** 4 (Suppl 1) Abs M1730

451315 **Reduced cumulative incidence of gastroduodenal ulcers with two doses of a new coxib, COX189 compared with standard therapeutic doses of ibuprofen in osteoarthritis patients.** Hawkey C & the PUCCINI Group *GASTROENTEROLOGY* 2002 **122** 4 (Suppl 1) Abs M1732

451430 **Lack of gastro-duodenal erosions in healthy subjects under treatment with COX189, a Cox-2 selective inhibitor.** Rordorf C, Scott G, Blood P, Milosavljev S, Kellet N, Mair S, Ford M *GASTROENTEROLOGY* 2002 **122** 4 (Suppl 1) Abs M902

451465 **Risk of cardiovascular events associated with selective COX-2 inhibitors.** Mukherjee D, Nissen SE, Topol EJ *J AM MED ASSOC* 2001 **286** 8 954-959
• *Results of a study which re-analyzed the available data on COX-2 inhibitors in the clinic and raised a cautionary flag about the risk of cardiovascular events with COX-2 inhibitors.*

451715 **Gastrointestinal safety studies highlight benefits of investigational COX-2 inhibitor.** Novartis AG *PRESS RELEASE* 2002 May 20

451842 **Digestive Disease Week 2002 (Part II) - OVERNIGHT REPORT, San Francisco, CA, USA.** Veryard C *IDDB MEETING REPORT* 2002 May 19-22
•• *Results presented at this meeting show that lumiracoxib is well tolerated and its GI safety profile is superior to conventional NSAIDs.*

451913 **Novartis launches TARGET, largest worldwide arthritis clinical trial.** Novartis Pharmaceuticals Corp *PRESS RELEASE* 2002 May 21

454848 **Data suggest that Prexige (lumiracoxib), a new COX-2 inhibitor, offers strong efficacy.** Novartis AG *PRESS RELEASE* 2002 June 13
•• *Report which indicates that lumiracoxib offers strong efficacy on the treatment of arthritis and pain with superior GI safety compared to traditional NSAIDs.*

455859 **Goldman Sachs Healthcare Conference - Growth momentum carries on.** Novartis AG *COMPANY PRESENTATION* 2002 June 11

458765 **Novartis sustains momentum: Double-digit growth in operating income in first half of 2002.** Novartis AG *PRESS RELEASE* 2002 July 22

466916 **New drugs in the R&D pipeline.** *PHARMA JPN* 2002 1815 October 14

467193 **Novartis looks ahead to continued dynamic launch program of innovative new medicines.** Novartis AG *PRESS RELEASE* 2002 October 17

468743 **Global Arthritis Research Network (GARN) meeting, April 4-7, 2002, Lucerne, Switzerland: COX-189: A novel COX-2 inhibitor.** Rheuma21st.com 2002 July 01 *http://www.rheuma21st.com/archive_index.html*

468857 **Cutting Edge reports: Future of cyclooxygenase inhibition: Where do we need to go?** Rheuma21st.com *INTERNET SITE* 2002 June 03 *http://www.rheuma21st.com/cutting_index.html*

468864 **Efficacy and safety of COX189 in osteoarthritis: A multi-national study.** Schnitzer TJ, Geusens P, Hasier P *ARTHRITIS RHEUM* 2001 **44** Suppl S336
•• *Results of a multinational, dose-ranging trial that revealed that lumiracoxib was comparable to diclofenac in the treatment of OA.*

468870 **Do NSAIDs affect the progression of osteoarthritis?** Ding C *INFLAMMATION* 2002 **26** 3 139-142

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468911 **Treatment of healthy subjects with COX189, a COX-2 selective inhibitor; endoscopic evidence for lack of gastro-duodenal erosions compared to non-selective NSAIDS.** Rordorf C, Scott G, Blood P, Milosavljev S, Branson J, Kellet N, Mair S, Ford M *INTERNET SITE* 2002 June 12-15 *http://www.hopkins-arthritis.som.jhmi.edu/edu/eular2002/oa-treatments.html*