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Metabolic Drugs

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Abstract

One of the *Annual Reviews* in this month's issue of **Drugs of the Future** is dedicated to updated information on metabolic drugs. The following table lists 70 drugs under development in this area, some of which have been published in previous issues of the journal and others that have been launched for an indication other than that discussed in the review. Information on the following 7 products is updated here: **ALX1-11, bazedoxifene acetate, ibandronate sodium, lasofoxifene tartrate, teriparatide, topiramate** and **zoledronic acid monohydrate.**

Once again, we remind our readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

Annual Review 2002: Metabolic Drugs

Drug	Source	Indication/Action	Phase
1426	Aventis Pharma	Antiobesity	II
1954	Aventis Pharma	Antiobesity	I
AdvaCAL[2]	Calcium Research Institute	Prevention of osteoporosis	II/III
Aldurazyme	Genzyme General/BioMarin	Inborn errors of metabolism	Prereg
ALX1-11[1]	NPS Allelix	Treatment of osteoporosis	III
Amfebutamone Hydrochloride[1,2]	Biovail/Glaxo	Antiobesity	III
AOD-9604	Metabolic Pharm.	Antiobesity	II
Ariplase	BioMarin	Inborn errors of metabolism	II
ATL-962	Alizyme	Antiobesity	II
Axokine	Emisphere/Regeneron	Antiobesity	III
Bay-39-9624	Bayer	Treatment of osteoporosis	I
Bazedoxifene Acetate[1]	Ligand/Wyeth	Treatment and prevention of osteoporosis	III
Bazedoxifene/Premarin	Wyeth Labs.	Treatment and prevention of osteoporosis	III
BVT-933	Biovitrum	Antiobesity	II
CAL	Chugai	Hypercalcemia	I
CDC-117	Celgene	Treatment of osteoporosis	I
Chrysalin	OrthoLogic	Bone repair	I/II
CHS-13340	Chugai	Treatment of osteoporosis	I
Dibotemin Alfa	Yamanouchi	Bone repair	Prereg
ED-71	Chugai	Treatment of osteoporosis	II
ETX-100	Exhale Therapeutics	Inborn errors of metabolism	I
Febuxostat[1]	Teijin/TAP	Gout	II
Flurbiprofen Nitroxybutyl Ester[1]	NicOx	Treatment of osteoporosis	II
GI-181771	Glaxo	Antiobesity	I
GW-320659	Glaxo	Antiobesity	II
Hectorol[2]	Bone Care International	Treatment of osteoporosis	II
HF-0299	Hunter-Fleming	Treatment of osteoporosis	I
HM-101	Hormos	Treatment and prevention of osteoporosis	I
Ibandronate Sodium[1,2]	Glaxo/Roche	Treatment of osteoporosis	III
Iduronate-2-Sulfatase	Transkaryotic Therapies	Inborn errors of metabolism	I/II
L-796568	Merck & Co.	Antiobesity	I
Lasofoxifene Tartrate[1]	Pfizer/Ligand	Prevention of osteoporosis	III
Lintitript	Sanofi-Synthélabo	Eating disorders	II
Minodronic Acid	Ono/Yamanouchi	Treatment of osteoporosis	II
MLN-4760	Millennium	Antiobesity	I
Nasal Calcitonin	Unigene	Treatment of osteoporosis	I
Ne-Osteo	Sulzer Biologics	Bone repair	III
OC-I Therapy	Aastrom	Treatment of osteoporosis	I/II
OGT-918	Oxford GlycoSciences	Gaucher's disease	Prereg
	Oxford GlycoSciences	Fabry's disease	I/II
ONO-4819	Ono	Bone repair	I
Oral Calcitonin	Nobex	Treatment osteoporosis	I
Ospemifene	Hormos	Treatment and prevention of osteoporosis	II
Ossigel	Orquest/Anika	Bone formation stimulant	II/III
Osteocel	Osiris	Bone repair	I
Osteoprotegerin	Amgen	Bone resorption inhibitor	II
Oxipurinol	Ilex	Uricosuric	II
P-57	Phytopharm/Pfizer	Antiobesity	II
Pegylated Axokine	Regeneron	Antiobesity	I
Pompase	Genzyme General	Inborn errors of metabolism	II/III
Puricase	Bio-Technology General	Uricosuric	I
Ranelic Acid Distrontium Salt	Servier	Prevention of osteoporosis	III
Recombinant Leptin	Amgen	Antiobesity	II
RF-1051	SuperGen	Antiobesity	II
rhBMP-2/ACS	Wyeth Pharmaceuticals	Bone repair	III
Rimonabant Hydrochloride	Sanofi-Synthélabo	Antiobesity	III
SB-418790	Glaxo	Antiobesity	I
SMP-536	Sumitomo Pharmaceuticals	Fabry's disease	II
Sodium Dichloroacetate	Questcor	Inborn errors of Metabolism	II/III
SomatoKine	Insmed	Treatment of osteoporosis	II
Squalamine	Genaera	Bone diseases	I
SR-586611	Sanofi-Synthélabo	Antiobesity	II

Continued

Annual Review 2002: Metabolic Drugs

Drug	Source	Indication/Action	Phase
Stannsoporfin	WellSpring Pharmaceutical	Hyperbilirubinemia	II
TAK-677	Takeda	Antiobesity	II
TAK-778	Takeda	Bone formation stimulant	II
Teriparatide[1]	Lilly	Treatment of osteoporosis	III
TH-9507	Theratechnologies	Bone diseases	II
Topiramate[1,2]	R.W. Johnson	Antiobesity	III
Uridine	Repligen	Inborn errors of metabolism	I
VR-1065	Vernalis/Roche	Antiobesity	I
Zoledronic Acid[1,2]	Novartis	Paget's disease	II
		Treatment of osteoporosis	III

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

ALX1-11

The recombinant human parathyroid hormone (rhPTH[1-84]) ALX1-11 (Preos™) is being evaluated in phase III clinical trials at NPS Pharmaceuticals for the treatment of osteoporosis.

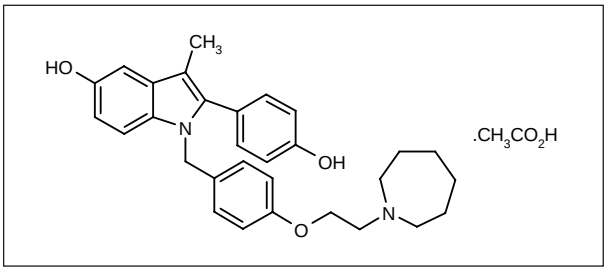
The TOP (Treatment of Osteoporosis with PTH) study is a multicenter, double-blind, placebo-controlled clinical trial designed to demonstrate the bone-building and fracture-reducing power of ALX1-11 in postmenopausal women who have low bone density and may have suffered a fracture, but who have not received drug therapy for osteoporosis. The clinical program also includes a study in women receiving hormone replacement therapy –the Europe-based POWER (PTH for Osteoporotic Women on Estrogen Replacement)– in which patients will receive daily s.c. injections of ALX1-11 or placebo in addition to their ongoing hormone replacement therapies for 24 months. ALX1-11 is also being assessed in combination with Merck & Co.'s Fosamax® (alendronate), a therapy that inhibits bone loss, in a fully enrolled 240-patient study sponsored by the National Institutes of Health (1, 2).

1. *NPS highlights key developments*. DailyDrugNews.com (Daily Essentials) April 3, 2002.

2. *Clinical program expanded for ALX1-11 in the treatment of osteoporosis*. DailyDrugNews.com (Daily Essentials) Nov 29, 2001.

Original monograph - Drugs Fut 2000, 25(10): 1007.

Bazedoxifene Acetate



Bazedoxifene acetate (TSE-424, WAY-140424) is a selective estrogen receptor modulator (SERM) with estrogen-agonist effects on bone and estrogen-antagonist effects on breast and endometrial tissue. The product was developed as part of a collaboration between Ligand and the former Wyeth-Ayerst division of American Home Products (now Wyeth) for the prevention and treatment of osteoporosis in postmenopausal women, as well as for vasomotor symptoms associated with menopause in combination with conjugated estrogens. Wyeth has initiated phase III clinical trials of bazedoxifene (1, 2).

A study in ovariectomized rats compared the effects on bone and the uterus of bazedoxifene, raloxifene and lasofoxifene. All three compounds displayed bone-sparing activity in this model, with more or less comparable effects on total body and lumber vertebral bone mineral density (BMD). However, bazedoxifene was superior to raloxifene in protecting cancellous bone. Also, unlike lasofoxifene, bazedoxifene was not associated with significant uterine stimulant effects at the optimal bone-sparing dose (3).

A randomized, open-label, crossover study in 12 healthy postmenopausal women assessed the pharmacokinetic interaction between single doses of bazedoxifene (20 mg p.o.) and ibuprofen (600 mg p.o.). The AUC and C_{max} values were 107 ng·h/ml and 118 ng/ml, respectively, for bazedoxifene, and 100 μg·h/ml and 106 μg/ml, respectively, for ibuprofen. Thus, the two compounds can be administered together with no need for dose adjustment (4).

The results from a prospective, double-blind, randomized trial in 360 healthy postmenopausal women with elevated urinary N-telopeptide levels comparing bazedoxifene (2.5-20 mg) to placebo and Premarin (conjugated equine estrogens)/medroxyprogesterone acetate (0.625-2.5 mg) for their effects on biochemical markers of bone metabolism were discussed at ENDO 2001. Although less active than Premarin/MPA, doses of 10 and 20 mg of bazedoxifene significantly reduced markers of bone resorption compared to placebo and were well tolerated. The dose-related reduction in bone remodeling seen for bazedoxifene confirms that it acts like an estrogen agonist on bone (5). The results of this study are summarized in Table I.

1. *Ligand receives milestone payment from Wyeth-Ayerst; TSE-424 development continues*. DailyDrugNews.com (Daily Essentials) Jan 10, 2001.

2. *Initiation of phase III trials of TSE-424 triggers milestone payment from Wyeth to Ligand*. DailyDrugNews.com (Daily Essentials) June 25, 2001.

3. Komm, B., Kharode, Y., Bex, Y. *Bazedoxifene acetate, a new tissue selective estrogen, preserves skeletal mass and vertebral compressive strength in the ovariectomized rat model (OVX) of osteopenia without uterine liability*. Osteoporosis Int 2002, 13(Suppl. 1): Abst P113SA.

4. Baird, S.J., McKeand, W.E., Ermer, J.C., Patat, A.A., Garcia-Quetglas, E. *Lack of clinically relevant pharmacokinetic interaction between bazedoxifene and ibuprofen*. Clin Pharmacol Ther 2002, 71(2): Abst WPIII-68.

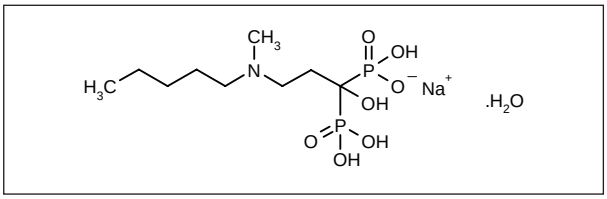
5. Ronkin, S., Baracat, E., Roma, L., Clarke, L., Boudes, P., Constantine, G., Lindsay, R. *TSE-424, a novel tissue selective estrogen, reduces biochemical indices of bone metabolism in a dose related fashion*. 83rd Annu Meet Endocr Soc (June 20-23, Denver) 2001, Abst P3-145.

Original monograph - Drugs Fut 2002, 27(2): 117.

Table I: Clinical study of bazedoxifene (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Menopause, osteoporosis	Randomized, double-blind	Bazedoxifene, 2.5 mg/day x 6 mo Bazedoxifene, 5 mg/day x 6 mo Bazedoxifene, 10 mg/day x 6 mo Bazedoxifene, 20 mg/day x 6 mo Conjugated equine estrogens, 0.625 mg + Medroxyprogesterone, 2.5 mg/day x 6 mo Placebo	360	Bazedoxifene up to 20 mg was safe and effective in bone resorption in postmenopausal women. A dose-related reduction in bone remodeling was observed	5

Ibandronate Sodium



The bisphosphonate ibandronate sodium, available since 1996 for the treatment of hypercalcemia, is being codeveloped by Roche and GlaxoSmithKline for the treatment and prevention of postmenopausal osteoporosis and is currently in phase III clinical trials for this indication. The first drug applications in the U.S. and Europe are expected to be filed this year, and both companies will copromote the product in all countries except Japan. Ibandronate has so far been evaluated in over 9000 patients, and a further clinical development program has been initiated in order to investigate innovative oral and intravenous intermittent dose regimens (1).

In the Oral Ibandronate Fracture Study, 2946 women at least 5 years beyond the onset of menopause and with a BMD T-score of < 2.0 SD at the lumbar spine were randomized to treatment with placebo or active drug. Ibandronate was administered either once daily (2.5 mg) or on a new dosing schedule, in which the drug was given on alternate days for 12 doses, repeated every 3 months. The total dose of ibandronate administered in the two active drug arms of the trial was comparable. All patients also received daily oral supplements of calcium and vitamin D. The primary endpoint of the study was a reduction in the incidence of new vertebral fractures after 3 years. The risk of radiologically verified vertebral fracture was reduced by 62% and 50% in the daily ibandronate and cyclical ibandronate treatment groups, respectively, as compared to placebo. A significant reduction in the risk of nonvertebral fractures was also obtained with ibandronate among a subgroup of patients with femoral neck BMD T-scores of < 3.0 SD. Markers of bone turnover were suppressed significantly and consistently with both bisphosphonate treatment regimens. The study drug was well tolerated in both groups, and the unique dosing schedule incorporating a prolonged drug-free interval was considered to be a convenient treatment alternative to existing bisphosphonate therapies (2). The results of this study and those that follow are summarized in Table II.

A study evaluating an alternative dosing regimen of ibandronate (3-monthly i.v. bolus injections) in the prevention of postmenopausal bone loss was reported by the Ibandronate Intravenous Study Group. This phase II/III study investigated the efficacy, safety and optimal dose of this regimen of ibandronate in 627 postmenopausal women. After 1 year, ibandronate produced significant and dose-dependent (0.5, 1 or 2 mg) increases in lumbar spine and hip BMD compared to baseline, with the greatest increase on the dose of 2 mg i.v. These increases correlated with dose-dependent and sustained decreases in bone turnover and therapy was well tolerated (3).

The Oral Ibandronate Study Group has reported that weekly dosing of oral ibandronate was preferable to daily administration of reference bisphosphonates, measured on the basis of patient preference, convenience and compliance. This multicenter, double-blind, placebo-controlled phase II/III trial enrolled 630 postmenopausal women who were treated with ibandronate (5, 10 or 20 mg) or placebo for 2 years. The study was designed to determine efficacy, safety and the optimum dose of once-weekly ibandronate for the prevention of osteoporosis. At the end of the 2-year treatment period, the investi-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Menopause, osteoporosis	Randomized, double-blind, multicenter	Ibandronate, 2.5 mg po od + Calcium, 500 mg/d po + Vitamin D, 400 IU/d po (n=982) Ibandronate, 20 mg po 1/48 h x 12 doses/3 mo + Calcium, 500 mg/d po + Vitamin D, 400 IU/d po (n=982) Placebo + Calcium, 500 mg/d po + Vitamin D, 400 IU/d po (n=982)	2946	Ibandronate was well tolerated and highly effective in reducing fractures associated with postmenopausal osteoporosis and can be administered with an extended drug-free interval	2
Menopause, osteoporosis	Randomized, double-blind, multicenter	Ibandronate, 0.5 mg iv bolus 1x/3 mo + Calcium, 500 mg/d po x 1 y (n=157) Ibandronate, 1 mg iv bolus 1x/3 mo + Calcium, 500 mg/d po x 1 y (n=156) Ibandronate, 2 mg iv bolus 1x/3 mo + Calcium, 500 mg/d po x 1 y (n=158) Placebo + Calcium, 500 mg/d po (n=156)	627	Ibandronate administered as 3-monthly i.v. bolus injections was well tolerated and showed a dose-dependent increase in spine and hip bone mineral density and a sustained reduction of bone turnover markers, with the 2-mg dose being the most effective	3
Menopause, osteoporosis	Randomized, double-blind, multicenter	Ibandronate, 5 mg po ow + Calcium, 500 mg/d po x 2 y (n=159) Ibandronate, 10 mg po ow + Calcium, 500 mg/d po x 2 y (n=154) Ibandronate, 20 mg po ow + Calcium, 500 mg/d po x 2 y (n=159) Placebo + Calcium, 500 mg/d po (n=158)	630	Oral weekly ibandronate was well tolerated and showed a dose-dependent increase in spine and hip bone mineral density, with the 20-mg dose producing the most substantial gains	4
Menopause, osteoporosis	Randomized, double-blind, multicenter	Ibandronate, 1 mg iv bolus 1x/3 mo + Calcium, 500 mg/d po + Vitamin D, 400 IU/d po x 1 y (n=131) Ibandronate, 2 mg iv bolus 1x/3 mo + Calcium, 500 mg/d po + Vitamin D, 400 IU/d po x 1 y (n=261) Placebo + Calcium, 500 mg/d po + Vitamin D, 400 IU/d po (n=128)	520	Ibandronate administered as 3-monthly i.v. 2-mg bolus injections was well tolerated and more effective than the 1-mg dose	5

gators determined that the most significant gains in BMD were obtained with the dose of 20 mg, although BMD was maintained with the 10-mg dose. Once-weekly ibandronate was well tolerated, and no safety concerns were reported (4).

A phase III study was conducted in 520 women with postmenopausal osteoporosis comparing the efficacy and safety of ibandronate 2 mg compared to 1 mg, given as a 3-monthly i.v. bolus injection. After 1 year, the higher dose increased lumbar spine BMD by 5% compared to 3% on the lower dose and 0.3% on placebo; the increase in BMD and suppression of bone markers on the dose of 2 mg i.v. were similar to those seen with oral ibandronate. The i.v. bolus injections were well tolerated and it was concluded that intermittent i.v. ibandronate offers a promising and convenient alternative to current oral bisphosphonate therapy (5).

1. *GSK and Roche to codevelop and copromote ibandronate*. DailyDrugNews.com (Daily Essentials) Dec 12, 2001.

2. Delmas, P., Recker, R., Stakkestad, J.A., Chestnut, C. III., Hoiseth, A., Weichselberger, A., Huss, H., Von Stein, T., Schimmer, R. *Oral ibandronate significantly reduces fracture risk in postmenopausal osteoporosis when administered daily or with a unique drug-free interval: Results from a pivotal phase III study*. Osteoporosis Int 2002, 13(Suppl. 1): Abst O37.

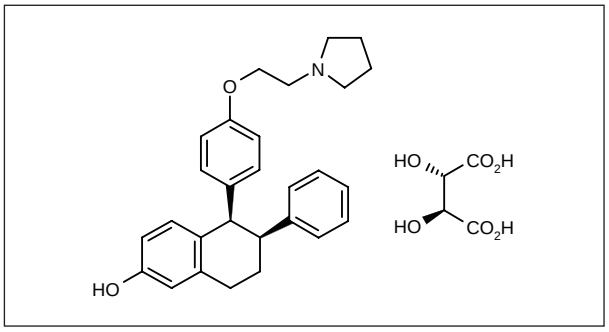
3. Stakkestad, J.A., Skag, A., Nordby, A., Burdeska, A., Jonkanski, I., Meinert, R. *Three-monthly intravenous ibandronate bolus injections: A novel treatment regimen to prevent postmenopausal bone loss*. Osteoporosis Int 2002, 13(Suppl. 1): Abst P43MO.

4. Felsenberg, D., Christiansen, C., Cerwinski, E., Burdeska, A., Johkanski, I., Meinert, R. *Weekly dosing of oral ibandronate is effective in the prevention of postmenopausal osteoporosis*. Osteoporosis Int 2002, 13(Suppl. 1): Abst P42SU.

5. Adami, S., Delmas, P., Felsenberg, D., Christiansen, C., Robinson, J., Coutant, K., Meinert, T., Schimmer, R., Von Stein, T. *Three-monthly 2 mg intravenous ibandronate bolus injections significantly increase bone mineral density in women with postmenopausal osteoporosis*. Osteoporosis Int 2002, 13(Suppl. 1): Abst O36.

Original monograph - Drugs Fut 1994, 19(1): 13.

Lasofoxifene Tartrate



Lasofoxifene tartrate (Pfizer), discovered as part of a collaboration with Ligand, is a next-generation selective estrogen receptor modulator (SERM) for the treatment and prevention of osteoporosis. A comprehensive phase III program is now under way.

Preclinical results obtained with lasofoxifene tartrate have highlighted its excellent pharmacokinetic and pharmacodynamic properties and improved efficacy as compared to earlier SERMs such as raloxifene. In ovariectomized rats and aged intact female rats, lasofoxifene blocked bone loss at doses as low as 10 mcg/kg/day p.o., compared to 500 μg/kg/day for raloxifene. Like estrogen, the study drug prevented bone loss by increasing apoptosis in osteoclasts. Lasofoxifene also reduced serum cholesterol levels in both male and female rodents at nearly the same doses required for bone preservation. In ovariectomized primates treated for 2 years, lasofoxifene inhibited bone turnover and prevented bone loss. In these preclinical models, no uterine hypertrophy was observed among animals treated with the agent (1).

Long-term (6 months) treatment of male rats with lasofoxifene preserved bone mass and strength by inhibiting age-related increases in bone resorption and bone turnover. The drug also reduced total serum cholesterol without affecting prostate weight, further supporting the use of SERMs for protecting elderly men from age-related changes in bone and serum cholesterol (2).

The ability of lasofoxifene to inhibit tumor development and the growth of established tumors in the *N*-nitroso-*N*-methylurea-induced rat mammary tumor model was evaluated. In the preventive study, lasofoxifene (0.1-10 mg/kg/day) caused a significant delay in tumor emergence equivalent to that of tamoxifen, with a 75% reduction in tumor incidence and a 90% reduction in total tumor number. It also reduced the multiplicity of tumors, resulting in a reduced total tumor burden. In the treatment study, 40% of drug-treated tumors regressed by greater than 50% at the highest dose (10 mg/kg/day). Lasofoxifene therefore has both chemopreventive and chemotherapeutic efficacy in this model (3).

A group at Wake Forest University has examined the effects of lasofoxifene on bone and the uterus in ovariectomized monkeys following reports of its ability to prevent bone loss without inducing uterine hypertrophy in ovariectomized rats. The osteopenia developing in ovariectomized adult female cynomolgus monkeys was prevented by 24 months of daily oral treatment with either conjugated equine estrogens (Premarin) or lasofoxifene (1 or 5 mg/kg). Also, the increase in bone remodeling associated with the reduction in spinal BMD induced by ovariectomy was prevented by both Premarin and lasofoxifene. However, in contrast to the uterine hypertrophy seen on Premarin, lasofoxifene maintained the reduction in uterine weight observed following ovariectomy. These results confirm the beneficial effects of lasofoxifene on bone turnover and bone loss and its lack of adverse effects on the uterus in primates (4).

The effects of lasofoxifene on bone loss were evaluated in a study in ovariectomized cynomolgus monkeys. Monkeys were placed into 1 of 5 groups: ovariectomized, sham-operated, ovariectomized plus Premarin 0.021 mg/kg p.o., ovariectomized plus lasofoxifene 1 mg/kg p.o. and ovariectomized plus lasofoxifene 5 mg/kg p.o. Once-daily treatment with lasofoxifene was shown to prevent bone loss due to ovariectomy in the lumbar vertebrae during the first 7 months of the study. Reduced bone biomarker and histomorphometric data indicated that the drug suppresses bone turnover and may be useful for the treatment of postmenopausal osteoporosis (5).

A review of phase I and II clinical trials conducted to date with lasofoxifene has demonstrated the SERM's good tolerability and favorable effects on bone and lipid metabolism in postmenopausal women. Six- and 12-month data demonstrate significant improvements in BMD of the spine and hip after 1 year of drug therapy as compared to placebo, as well as sustained reductions in LDL cholesterol as early as 6 weeks after starting treatment and lasting for up to 1 year. The drug has been administered safely for 1 year at doses up to 10 mg/day, with no endometrial atypia, hyperplasia or cancer detected in any subject treated (6). The results of this study are summarized in Table III.

Watson Pharmaceuticals has claimed pharmaceutical compositions and devices for the transdermal delivery of lasofoxifene. These devices may be in the form of matrix or reservoir patches (7).

1. Thompson, D.D. *Discovery of lasofoxifene: The next generation of SERMs and the lasofoxifene pre-clinical evaluation.* Osteoporosis Int 2002, 13(Suppl. 1): Abst SY3.

2. Ke, H.Z., Qi, H., Chidsey-Frink, K.L., Crawford, D.T., Thompson, D.D. *Lasofoxifene (CP-336,156) protects against the age-related changes in bone mass, bone strength, and total serum cholesterol in intact aged male rats.* J Bone Miner Res 2001, 16(4): 765.

Table III: Clinical study of lasofoxifene (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Menopause	Pooled	Phase I: Lasofoxifene, 1-100 mg sd Lasofoxifene, 0.01-20 mg od x 2 wk Phase II: Lasofoxifene, 0.017-10 mg od x 1 [max] y Placebo	1126	Lasofoxifene was well tolerated and improved bone and lipid metabolism in postmenopausal women	6

3. Cohen, L.A., Pittman, B., Wang, C.-X., Aliaga, C., Yu, L., Moyer, J.D. *LAS, a novel selective estrogen receptor modulator with chemopreventive and therapeutic activity in the N-nitroso-N-methylurea-induced rat mammary tumor model*. Cancer Res 2001, 61(24): 8683.

4. Brommage, R., Hotchkiss, C.E., Stancill, M.W., Lees, C.J. *Lasofoxifene inhibits bone turnover and maintains spine BMD after ovariectomy in monkeys*. Bone 2001, 28(5, Suppl.): Abst P594 S.

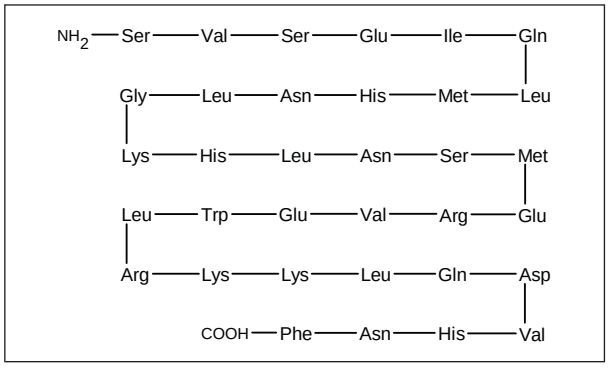
5. Lees, C.J., Hotchkiss, C.E., Brommage, R. *Lasofoxifene prevents ovariectomy-induced skeletal changes in macaques*. 83rd Annu Meet Endocr Soc (June 20-23, Denver) 2001, Abst P3-140.

6. Moffett, A. Jr. et al. *Emerging data and experience with lasofoxifene: Highlights from clinical trials*. Osteoporosis Int 2002, 13(Suppl. 1): Abst SY4.

7. Fikstd, D., Quan, D. (Watson Pharmaceuticals, Inc.). *Transdermal delivery of lasofoxifene*. WO 0191724.

Original monograph - Drugs Fut 1998, 23(10): 1066.

Teriparatide



Lilly's investigational recombinant human parathyroid hormone (rhPTH[1-34]) teriparatide (LY-333334, Forteo™) was demonstrated in a pivotal phase III study presented at the IBMS/ECTS meeting last year to significantly reduce the risk of spinal and nonspinal fractures and to improve cortical bone strength among postmenopausal women with a history of osteoporosis-related fractures.

Teriparatide was recommended for approval last year by the FDA's Endocrinologic and Metabolic Drugs Advisory Committee as a treatment for osteoporosis in postmenopausal women and the committee also issued a 5-5 split vote on its recommendation of teriparatide to increase bone mass in men with osteoporosis. In contrast to currently approved osteoporosis therapies which slow or stop bone loss, teriparatide actually stimulates new bone formation by increasing the number and/or activity of osteoblasts (1-5). Lilly is also developing an inhalable formulation of teriparatide with Inhale (6), as well as oral formulations with Emisphere (7).

Digital X-ray radiogrammetry (DXR) was used in a pilot study to measure changes in cortical thickness associated with teriparatide treatment in women with osteoporosis. DXR was performed on the radius, ulna and three middle metacarpals at baseline and at 1 year on 40 patients from a large, double-blind, randomized study who received either placebo or teriparatide 20 or 40 mcg once daily. The combined measurements showed that teriparatide increased the outer diameter and decreased the inner diameter compared to placebo. Cortical thickness tended to decrease in the placebo group and increase in the teriparatide-treated groups. The outer and inner bone diameters expanded, however, in patients with hyperparathyroidism. It was concluded that increases in cortical thickness due to teriparatide treatment could be detected by the technique and may be useful in assessing bone strength independent of bone mineral density (BMD) (8). The results of this study and some that follow are summarized in Table IV.

A pilot study has evaluated the effects of teriparatide treatment on cortical bone thickness and area using peripheral quantitative computed tomography (pQCT) on women randomized to placebo or 20 or 40 mcg of teriparatide once daily as part of a large multicenter study. Teriparatide-treated patients were found to have greater periosteal circumference and cortical area, similar bone mineral content and lower bone density than those given placebo. Teriparatide-treated patients had greater polar and axial moments of inertia and torsional bone strength index. The greater periosteal distribution of cortical bone detected by pQCT may, in part, explain the reduction in nonvertebral fractures seen with teriparatide treatment (9).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Osteoporosis, post-menopausal	Randomized, double-blind, multicenter	Teriparatide, 20 μg od x 1 y Teriparatide, 40 μg od x 1 y Placebo	40	Teriparatide increased bone strength in postmenopausal patients by increasing cortical bone thickness, as shown by a higher outer diameter and a lower inner diameter measured by digital X-ray radiogrammetry in the radius, ulna and three middle metacarpals	8
Osteoporosis, post-menopausal	Randomized, double-blind, multicenter	Teriparatide, 20 μg od x 21 mo [median] Teriparatide, 40 μg od x 21 mo [median] Placebo	101	Treatment with teriparatide promoted bone modeling and intracortical remodeling, as evidenced by an increase in the periosteal circumference and cortical area of the proximal radius from postmenopausal women. These changes may contribute towards decreasing the number of nonvertebral fractures in these patients	9
Osteoporosis	Randomized, double-blind	Teriparatide, 20 μg/d sc x 11 mo (median) Teriparatide, 40 μg/d sc x 11 mo (median) Placebo	437	Teriparatide rapidly increased lumbar spine bone mineral density in men regardless of age, fracture history, sex steroid levels, smoking or alcohol intake	12-14
Menopause, osteoporosis	Randomized, double-blind, multicenter	Teriparatide, 20 μg od x 21 mo [median] + Calcium, 1000 mg od + Vitamin D, 400-1200 IU od Teriparatide, 40 μg od x 21 mo [median] + Calcium, 1000 mg od + Vitamin D, 400-1200 IU od Placebo	1637	Teriparatide 20 μg or 40 μg was safe, well tolerated and reduced the risk of vertebral and nonvertebral fractures by 35% and 40%, respectively, and increased total-body, lumbar spine and femoral neck bone mineral density	15-17
Osteoporosis, post-menopausal	Randomized, double-blind	Teriparatide, 20 μg od x 19 mo [mean] Teriparatide, 40 μg od x 19 mo [mean] Placebo	1262	The absolute risk for vertebral fractures in postmenopausal women decreased after treatment with 20 μg or 40 μg of teriparatide. This reduction was maintained during the 18-month observation period, thus suggesting that teriparatide had durable effects even after treatment had been stopped	18
Menopause, osteoporosis	Randomized	Teriparatide, 40 μg od sc x 15 mo (median) (n=122) Placebo (n=125)	247	The combination of teriparatide and either ongoing or *de novo* HRT significantly increased bone mineral density at the lumbar spine and proximal femur compared to HRT alone	19, 20
Osteoporosis	Open	Teriparatide, 80 μg sc od x 3 mo → Teriparatide, 32 μg sc bid x 3 mo → Calcium, 1150 mg bid+ Calcitriol, 0.5 μg bid	1	Treatment with teriparatide for 6 months increased the patient's lumbar bone mineral density by 23% compared to baseline. Teriparatide was thus effective as a therapy for adolescent osteoporosis	21
Osteoporosis, post-menopausal	Randomized, double-blind	Teriparatide, 40 μg od x 14 mo [mean] (n=73) Alendronate, 10 μg od x 14 mo [mean] (n=73)	146	Treatment with 40 μg teriparatide for 14 months increased bone formation and bone resorption markers. Patients treated with teriparatide showed a greater and more rapid increase in bone mass density than those treated with alendronate	22
Menopause, osteoporosis	Open	Teriparatide, 400 U/d x 18 mo (men) or x 36 mo (women)		Teriparatide demonstrated anabolic activity on cortical and cancellous bone in the iliac crest and improved cancellous bone microarchitecture	23

The effects of teriparatide on bone mass, remodeling and strength were examined in cortical bone of rabbits treated *in vivo* with the agent (10 μg/kg s.c.) for 30 or 70 days. Treatment significantly increased the intracortical activation frequency of cortical bone in the tibial midshaft at 35 days. Animals treated for 30 or 70 days also displayed significantly greater cortical area and bone strength. No changes in porosity were observed with treatment (10).

Teriparatide 5, 30 and 75 μg/kg was administered to rats for 2 years. While bone mass increased substantially, bone proliferative lesions were also seen and osteosarcoma was common, especially in the higher dose groups. It was concluded that the bone tumors likely resulted from the long period of treatment and do not indicate an increased risk of bone cancer in humans treated with PTH (11).

A prospective, double-blind, randomized, placebo-controlled pivotal phase III trial was conducted in men with osteoporosis, followed by an 18-month posttreatment observational study. The trial enrolled 437 males with idiopathic or hypogonadal osteoporosis who self-injected teriparatide 20 or 40 μg, or placebo, daily for about 11 months. The vertebral BMD at the lumbar spine and hip increased significantly and rapidly, as early as 3 months, on teriparatide compared to placebo, with no apparent dose-response effect. Furthermore, the response to teriparatide was not affected by age, history of previous fracture, sex steroid levels or smoking or alcohol intake. In the observational study, patients who had received therapy with teriparatide showed a reduction in the risk of moderate or severe spinal fractures of 83% during the entire observation period; these fractures occurred in only 1% of those taking teriparatide compared to 7% on placebo (12-14).

A double-blind, randomized, placebo-controlled study of teriparatide was carried out in 1637 postmenopausal women with osteoporosis and prior vertebral fractures to assess the relationship between radiographic vertebral fracture grade and clinical sequelae of fracture. Patients were treated with either placebo or 20 or 40 μg of teriparatide by injection once daily in addition to receiving supplemental calcium and vitamin D. After a median follow-up of 21 months, it was found that the risk relative to placebo for vertebral fracture in the teriparatide 20 and 40 μg groups was 0.35 and 0.31, respectively. For women with 1 or more moderate or severe fractures, the fracture risk as compared with placebo was 0.10 and 0.22 for the 20- and 40-μg groups, respectively. The risk of nonvertebral fractures was also reduced with treatment (relative risk of 0.65 and 0.60, respectively, for 20 and 40 μg *vs.* placebo). Significantly fewer teriparatide-treated patients had new moderate or severe vertebral fractures. The incidence and severity of clinical sequelae were also reduced in the teriparatide treatment groups and the side effects were minor (15-17). A group of 1262 women from this study volunteered for an 18-month observation study following discontinuation of teriparatide. The patients had originally shown a significant reduction in vertebral fractures (65-69%) and increases in lumbar spine BMD on teriparatide. Following discontinuation, 29% and 54% were reportedly using other therapies for osteoporosis at 6 and 18 months, respectively. During the treatment period, an absolute risk reduction for at least 1 incident vertebral fracture of 9% and 10%, respectively, was observed in the teriparatide 20- and 40-μg groups, and at 18 months after stopping treatment the absolute risk reduction was 13% at both doses. Absolute risk reductions of 8% and 6%, respectively, were obtained on teriparatide 20 and 40 μg as regards new moderate and severe fractures, and the absolute risk reduction at 18 months of observation was 11%. This study thus provides evidence indicating that the beneficial effect of teriparatidse on vertebral fractures is maintained even after stopping treatment (18).

Teriparatide 40 μg/day s.c. was evaluated in 247 postmenopausal women with osteopenia or osteoporosis who were taking or began hormone replacement therapy (HRT). Patients were randomized to teriparatide or placebo for a median of 16 months. Neither ongoing nor *de novo* HRT altered the effect of teriparatide on BMD at the lumbar spine and proximal femur (19, 20).

Parathyroid hormone (PTH) 1-34 replacement therapy with teriparatide rapidly normalized lumbar bone mass in a 16-year-old girl with autoimmune polyglandular syndrome type 1 with hypoparathyroidism and osteoporosis (21).

A double-blind, randomized, placebo-controlled trial compared the effects of teriparatide (40 μg) and alendronate sodium (10 mg) on markers of bone metabolism in postmenopausal women with osteoporosis treated for a median of 14 months. The results showed that teriparatide stimulated new bone formation and bone remodeling and resulted in greater and more rapid increases in BMD compared to the bone resorption inhibitor (22).

Treatment of patients with osteoporosis with teriparatide was assessed in 8 men and 8 postmenopausal women. Patients were given daily injections of teriparatide 400 U for 18 months (men) or 36 months (women). Paired iliac crest bone biopsies from before and after treatment were analyzed. The treatment had an anabolic action on cortical and cancellous bone. Cortical porosity did not increase, and 3D trabecular connectivity increased in most patients (23).

Parathyroid hormone has been found to reduce the risk of cancer, particularly breast, skin, bladder and gastric carcinomas, preferably breast carcinoma, including subjects with a relatively low risk or high risk of osteoporosis. The preferred hormone is human PTH(1-34) or its recombinant form teriparatide (24).

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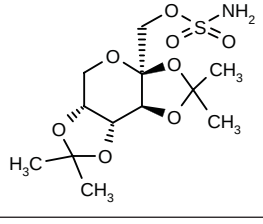
Topiramate



Topiramate (Johnson & Johnson's Topamax®) is a known anticonvulsant which has been investigated for a number of other indications, including eating disorders.

A retrospective study in 18 outpatients treated with topiramate found no significant relationship between weight loss and drug blood levels or effective dose. Treatment was begun at 12.5 mg and titrated up to an effective dose (mean 644.44 ± 263.96 mg). The average blood level of topiramate was 17.34 ± 6.37 and the average weight loss was 5.22 ± 5.38 kg (1).

The effects of topiramate at doses of 64, 96, 192 or 384 mg/day were compared with placebo in a multicenter, double-blind, randomized trial conducted in 385 nondiabetic obese subjects. Administration of topiramate for 24 weeks induced a dose-dependent decrease in body weight and reduced blood pressure. The following adverse events were more frequent with topiramate than with placebo: paresthesias, memory disturbances,

fatigue, somnolence, appetite loss, taste perversion, concentration disturbances and dizziness (2).

The treatment of binge-eating disorder with topiramate was assessed in a 22-year-old woman (109 kg) with no neuropsychiatric comorbidity, who had been overweight since age 18 and who had not responded to other treatments. An initial dose of 25 mg b.i.d. for 2 weeks was followed by an increase of 25 mg every week until a target dose of 75 mg b.i.d. was attained. A marked reduction from 4 days to 1 day of binge eating per week was observed after 2 weeks, and the total number of episodes dropped from 8 to 2 per week. No more episodes were recorded from the first until the fourth month of treatment and her weight dropped to 98.6 kg (3).

In an open clinical trial, 8 obese patients with binge-eating disorder were treated with topiramate 150 mg/day for 16 weeks. The treatment reduced binge eating in all patients who completed the trial (6), with 4 patients achieving total remission and 2 a notable reduction in the frequency of binge eating (4).

The ability of topiramate to normalize weight gain resulting from therapy with antipsychotic agents was assessed in a 32-year-old female with a schizoaffective disorder who had gained 36 kg over 3 years following olanzapine (20 mg/day) therapy. Topiramate was initiated at 25 mg/day and titrated up to 150 mg/day. A dramatic reduction in binging episodes and an average weight loss of 2.3 kg/week were obtained. Six months after topiramate discontinuation, the patient had maintained an average weight of 70.5 kg, while still receiving 20 mg/day olanzapine. Psychotic and mood symptoms remained under control (5).

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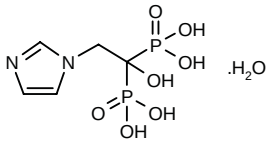
Zoledronic Acid Monohydrate



Currently marketed (Novartis's Zometa®) for the treatment of hypercalcemia of malignancy, or tumor-induced hypercalcemia, the potent parenteral bisphosphonate zoledronic acid was subsequently approved for the treatment of multiple myeloma and bone metastases associated with solid tumors such as prostate, lung and breast cancer. The 15-min infusion time of zoledronic acid offers a significant advantage compared to the 2-4 h required for infusion of pamidronate disodium (Aredia®), the current standard of care (1-10). Clinical trials are also under way in women with postmenopausal osteoporosis.

Results from 2 parallel, multicenter, randomized, double-blind studies conducted in 287 patients with moderate to severe hypercalcemia of malignancy showed that single-dose (4 or 8 mg by 5-min infusion) zoledronic acid was superior to pamidronate (90 mg by 2-h infusion). On day 10, complete responses were seen in 88.4% and 86.7% of the patients treated with 4 and 8 mg zoledronic acid compared to 69.7% of the patients treated with pamidronate. The median duration of complete responses was 32, 43 and 18 days for 4 and 8 mg zoledronic acid and pamidronate, respectively. About 50% of the zoledronic acid-treated patients as compared to 33.3% of the pamidronate-treated patients showed normalization of corrected serum calcium by day 4 (11).

The pharmacokinetics and safety of zoledronic acid (4 mg by 15-min i.v. infusion every 28 days) were determined after administration of 3 doses in a study involving 19 cancer patients (multiple myeloma, prostate, breast and other) with bone metastases and normal or mildly or moderately impaired renal function. The agent was well tolerated, with no clinically significant effects on renal function. Of the 33 serious adverse events reported, none were related to zoledronic acid. Those adverse events thought to be due to underlying disease or zoledronic acid were bone pain, fatigue, pyrexia, nausea and myalgia. Results from 4 patients with normal renal function administered [^{14}C]-labeled zoledronic acid as the first dose showed that the agent is metabolically stable and did not accumulate with multiple dosing. No clinically significant changes in the pharmacokinetics of the agent were observed between patients with normal and impaired renal function, suggesting that no dose adjustments are required in these patients (12).

A double-blind, randomized, placebo-controlled phase III trial was conducted in 643 men with hormone-

Table V: Clinical study of zoledronic acid (Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Bone cancer, prostate cancer metastatic to bone	Randomized, double-blind, multicenter	Zoledronic acid, 4 mg iv over 15 min 1x/3 wk x 15 mo Zoledronic acid, 8/4 mg iv over 15 min 1x/3wk x 15 mo Placebo	643	Zoledronic acid reduced the risk of pathologic fractures and other skeletal-related events in patients with hormone-refractory prostate cancer with at least one bone metastasis	13

refractory prostate cancer and at least 1 bone metastasis to assess the clinical benefits of zoledronic acid (4 or 8/4 mg once every 3 weeks for 15 months) administration. Zoledronic acid decreased the overall incidence of long bone and vertebral fractures, while proving as safe as other bisphosphonates. Compared to placebo, treatment with zoledronic acid was associated with a number of beneficial effects, *i.e.*, decrease in the rate of skeletal-related events (SRE), pathological fractures and skeletal morbidity, and also a delay in the time to the first SRE or pathological fracture. The results were similar for both dosing regimens (13, 14). The results of this study are summarized in Table V.

An ongoing trial has enrolled 55 breast cancer patients with skeletal metastases who are to receive zoledronic acid 4 mg every 4 weeks either at home or in the hospital. Results from the hospital run-in phase include significant improvements in quality of life and pain after 2 infusions of the drug (15).

Zoledronic acid was examined in a placebo-controlled phase II study in 351 postmenopausal women with low bone density given different doses and treatment regimens of the drug by i.v. injection. Five regimens were tested over 1 year: 0.25, 0.5 or 1 mg every 3 months, 2 mg every 6 months and a single annual dose of 4 mg. The primary endpoint was lumbar spine BMD. All zoledronic acid groups showed similar increases in BMD for the spine, which was 4.3-5.1% higher than in the placebo group; similarly, BMD in the femoral neck was 3.1-3.5% higher on zoledronic acid than on placebo. Also, significant suppression of biochemical markers of bone resorption was seen after 1 year of zoledronic acid treatment, regardless of the dose or regimen. Although myalgia and pyrexia were reported more frequently in the zoledronic acid groups, withdrawal rates due to adverse events were not different between zoledronic acid and placebo. Zoledronic acid administered at intervals of 6-12 months would thus appear to be an effective treatment alternative for postmenopausal osteoporosis and is furthermore expected to improve compliance as compared to current daily oral therapy, although further studies will be necessary (16).

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