PDR®
57
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PHYSICIANS' DESK REFERENCE®

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VICOPROFEN, like other drugs containing ibuprofen, is not free of side effects The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes Patients should be instructed to report any signs and symptoms of gastrointestinal bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Laboratory Tests

A decrease in hemoglobin may occur during VICOPROFEN therapy, and elevations of liver enzymes may be seen in a small percentage of patients during VICOPROFEN therapy (see PRECAUTIONS - Hematological Effects and PRECAUTIONS - Hepatic Effects).

In patients with severe hepatic or renal disease, effects of therapy should be monitored with liver and/or renal function tests.

Drug Interactions

ACE-inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking VICOPROFEN concomitantly with ACE-inhibitors.

Anticholinergics: The concurrent use of anticholinergics with hydrocodone preparations may produce paralytic ileus.

Antidepressants: The use of MAO inhibitors or tricyclic antidepressants with VICOPROFEN may increase the effect of either the antidepressant or hydrocodone.

Aspirin: As with other products containing NSAIDs, concomitant administration of VICOPROFEN and aspirin is not generally recommended because of the potential of increased adverse effects

CNS Depressants: Patients receiving other opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with VICOPROFEN may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

Furosemide: Ibuprofen has been shown to reduce the natriuretic effect of furosemide and thiazides in some patients This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with VICOPROFEN the patient should be observed closely for signs of renal failure (see PRECAUTIONS - Renal Effects), as well as diuretic efficacy

Lithium: Ibuprofen has been shown to elevate plasma lithium concentration and reduce renal lithium clearance. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when VICOPROFEN and lithium are administered concurrently, patients should be observed for signs of lithium toxicity.

Methotrexate: Ibuprofen, as well as other NSAIDs, has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used when VICOPROFEN is administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

The carcinogenic and mutagenic potential of VICOPROFEN has not been investigated. The ability of VICOPROFEN to impair fertility has not been assessed

Pregnancy: Pregnancy Category C.

Teratogenic Effects: VICOPROFEN, administered to rabbits at 95 mg/kg (5.72 and 1 9 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, resulted in an increase in the percentage of litters and fetuses with any major abnormality and an increase in the number of litters and fetuses with one or more nonossified metacarpals (a minor abnormality). VICOPROFEN, administered to rats at 166 mg/kg (10.0 and 1.66 times the maximum clinical dose based on body weight and surface area, respectively), a maternally toxic dose, did not result in any reproductive toxicity There are no adequate and well-controlled studies in pregnant women. VICOPROFEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided. Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal

Labor and Delivery

As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of VICOPROFEN is not recommended during labor and delivery

Nursing Mothers

It is not known whether hydrocodone is excreted in human milk. In limited studies, an assay capable of detecting 1 mcg/mL did not demonstrate ibuprofen in the milk of lactating mothers. However, because of the limited nature of the studies, and the possible adverse effects of prostaglandin-inhibiting drugs on neonates, VICOPROFEN is not recommended for use in nursing mothers.

Pediatric Use

The safety and effectiveness of VICOPROFEN in pediatric patients below the age of 16 have not been established.

Geriatric Use

In controlled clinical trials there was no difference in tolerability between patients < 65 years of age and those ≥ 65, apart from an increased tendency of the elderly to develop constipation However, because the elderly may be more sensitive to the renal and gastrointestinal effects of nonsteroidal anti-inflammatory agents as well as possible increased risk of respiratory depression with opioids, extra caution and reduced dosages should be used when treating the elderly with VICOPROFEN.

ADVERSE REACTIONS

VICOPROFEN was administered to approximately 300 pain patients in a safety study that employed dosages and a duration of treatment sufficient to encompass the recommended usage (see DOSAGE AND ADMINISTRATION). Adverse event rates generally increased with increasing daily dose. The event rates reported below are from approximately 150 patients who were in a group that received one tablet of VICOPROFEN an average of three to four times daily. The overall incidence rates of adverse experiences in the trials were fairly similar for this patient group and those who received the comparison treatment, acetaminophen 600 mg with codeine 60 mg.

The following lists adverse events that occurred with an incidence of 1% or greater in clinical trials of VICOPROFEN, without regard to the causal relationship of the events to the drug To distinguish different rates of occurrence in clinical studies, the adverse events are listed as follows:

name of adverse event = less than 3%

adverse events marked with an asterisk * = 3% to 9%

adverse event rates over 9% are in parentheses.

Body as a Whole: Abdominal pain*; Asthenia*; Fever, Flu syndrome; Headache (27%); Infection*; Pain.

Cardiovascular: Palpitations; Vasodilation

Central Nervous System: Anxiety*; Confusion; Dizziness (14%); Hypertonia; Insomnia*; Nervousness*; Paresthesia; Somnolence (22%); Thinking abnormalities.

Digestive: Anorexia; Constipation (22%); Diarrhea*; Dry mouth*, Dyspepsia (12%); Flatulence*, Gastritis; Melena; Mouth ulcers; Nausea (21%); Thirst; Vomiting*.

Metabolic and Nutritional Disorders: Edema*.

Respiratory: Dyspnea; Hiccups; Pharyngitis; Rhinitis.

Skin and Appendages: Pruritus*, Sweating*

Special Senses: Tinnitus.

Urogenital: Urinary frequency.

Incidence less than 1%

Body as a Whole: Allergic reaction.

Cardiovascular: Arrhythmia, Hypotension; Tachycardia.

Central Nervous System: Agitation; Abnormal dreams; Decreased libido, Depression, Euphoria; Mood changes; Neuralgia; Slurred speech; Tremor, Vertigo.

Digestive: Chalky stool; "Clenching teeth"; Dysphagia; Esophageal spasm; Esophagitis; Gastroenteritis, Glossitis, Liver enzyme elevation.

Metabolic and Nutritional: Weight decrease

Musculoskeletal: Arthralgia; Myalgia.

Respiratory: Asthma; Bronchitis; Hoarseness, Increased cough, Pulmonary congestion; Pneumonia; Shallow breathing; Sinusitis.

Skin and Appendages: Rash; Urticaria.

Special Senses: Altered vision; Bad taste; Dry eyes.

Urogenital: Cystitis, Glycosuria, Impotence; Urinary incontinence; Urinary retention.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: VICOPROFEN Tablets are a Schedule III controlled substance

Abuse: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of opioids; therefore, VICOPROFEN Tablets should be prescribed and administered with the same degree of caution appropriate to use of other oral narcotic medications.

Dependence: Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome; assumes clinically significant proportions only after several weeks of continued opioid use, although a mild degree of physical dependence may develop after a few days of opioid therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients However, psychic dependence is unlikely to develop when VICOPROFEN Tablets are used for a short time for the treatment of acute pain.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone and/or ibuprofen.

Signs and Symptoms:

Hydrocodone component: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur

Ibuprofen component: Symptoms include gastrointestinal irritation with erosion and hemorrhage or perforation, kidney damage, liver damage, heart damage, hemolytic anemia, agranulocytosis, thrombocytopenia, aplastic anemia, and meningitis Other symptoms may include headache, dizziness, tinnitus, confusion, blurred vision, mental disturbances, skin rash, stomatitis, edema, reduced retinal sensitivity, corneal deposits, and hyperkalemia.

Treatment:

Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose or unusual sensitivity to opioids, including hydrocodone. Therefore, an appropriate dose of naloxone hydrochloride should be administered intravenously with simultaneous efforts at respiratory resuscitation. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. Supportive measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug. In cases where consciousness is impaired it may be inadvisable to perform gastric lavage If gastric lavage is performed, little drug will likely be recovered if more than an hour has elapsed since ingestion. Ibuprofen is acidic and is excreted in the urine; therefore, it may be beneficial to administer alkali and induce diuresis. In addition to supportive measures the use of oral activated charcoal may help to reduce the absorption and reabsorption of ibuprofen. Dialysis is not likely to be effective for removal of ibuprofen because it is very highly bound to plasma proteins.

DOSAGE AND ADMINISTRATION

For the short-term (generally less than 10 days) management of acute pain, the recommended dose of VICOPROFEN is one tablet every 4 to 6 hours, as necessary. Dosage should not exceed 5 tablets in a 24-hour period. It should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The lowest effective dose or the longest dosing interval should be sought for each patient, especially in the elderly. After observing the initial response to therapy with VICOPROFEN, the dose and frequency of dosing should be adjusted to suit the individual patient's need, without exceeding the total daily dose recommended.

HOW SUPPLIED

VICOPROFEN® tablets are available as:

White film-coated round convex tablets, engraved with "VP" over ℞ on one side and plain on the other side

Bottles of 100-NDC 0074-2277-14

Bottles of 500-NDC 0074-2277-54

Hospital Unit Dosage Package-100 tablets (4×25 tablets)-NDC 0074-2277-12

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container.

A Schedule Ⓒ Narcotic

Revised: August, 2001

Ref. 03-5136

ABBOTT LABORATORIES

NORTH CHICAGO, IL 60064, U.S.A PRINTED IN U.S.A.

Shown in Product Identification Guide, page 304

ZEMPLAR™

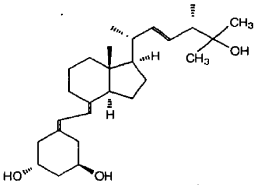
(paricalcitol injection)

Fliptop Vial

DESCRIPTION

Zemplar™ (paricalcitol injection) is a synthetically manufactured vitamin D analog It is available as a sterile, clear, colorless, aqueous solution for intravenous injection. Each mL contains paricalcitol, 5 mcg; propylene glycol, 30% (v/v); and alcohol, 20% (v/v).

Paricalcitol is a white powder chemically designated as 19-nor-1α,3β,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene and has the following structural formula:



Molecular formula is $C_{27}H_{44}O_3$.

Molecular weight is 416 65.

CLINICAL PHARMACOLOGY

Mechanism of Action

Paricalcitol is a synthetic vitamin D analog Vitamin D and paricalcitol have been shown to reduce parathyroid hormone (PTH) levels.

Continued on next page

Zemplar—Cont.

Pharmacokinetics

Distribution

The pharmacokinetics of paricalcitol have been studied in patients with chronic renal failure (CRF) requiring hemodialysis. Zemplar™ is administered as an intravenous bolus injection. Within two hours after administering doses ranging from 0.04 to 0.24 mcg/kg, concentrations of paricalcitol decreased rapidly; thereafter, concentrations of paricalcitol declined log-linearly with a mean half-life of about 15 hours. No accumulation of paricalcitol was observed with multiple dosing.

Elimination

In healthy subjects, plasma radioactivity after a single 0.16 mcg/kg intravenous bolus dose of ^{3}H-paricalcitol (n=4) was attributed to parent drug. Paricalcitol was eliminated primarily by hepatobiliary excretion, as 74% of the radioactive dose was recovered in feces and only 16% was found in urine.

Metabolism

Several unknown metabolites were detected in both the urine and feces, with no detectable paricalcitol in the urine. These metabolites have not been characterized and have not been identified. Together, these metabolites contributed 51% of the urinary radioactivity and 59% of the fecal radioactivity. *In vitro* plasma protein binding of paricalcitol was extensive (>99.9%) and nonsaturable over the concentration range of 1 to 100 ng/mL.

Paricalcitol Pharmacokinetic Characteristics in CRF Patients (0.24 mcg/kg dose)

Parameter	n	Values (Mean ± SD)
C_{max} (5 min. after bolus)	6	1850 ± 664 (pg/mL)
$AUC_{0-\infty}$	5	27382 ± 8230 (pg•hr/mL)
CL	5	0.72 ± 0.24 (L/hr)
V_{ss}	5	6 ± 2 (L)

Laboratory Tests

In placebo-controlled studies, paricalcitol reduced serum total alkaline phosphatase levels.

Special Populations

Paricalcitol pharmacokinetics have not been investigated in special populations (geriatric, pediatric, hepatic insufficiency), or for drug-drug interactions. Pharmacokinetics were not gender-dependent.

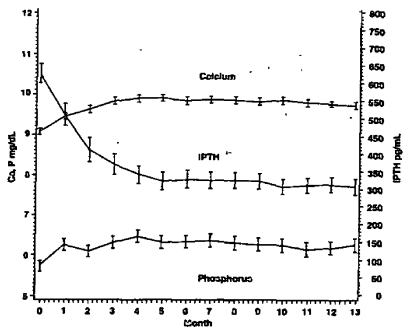
Clinical Studies

In three 12-week, placebo-controlled, phase 3 studies in chronic renal failure patients on dialysis, the dose of Zemplar™ was started at 0.04 mcg/kg 3 times per week. The dose was increased by 0.04 mcg/kg every 2 weeks until intact parathyroid hormone (iPTH) levels were decreased at least 30% from baseline or a fifth escalation brought the dose to 0.24 mcg/kg, or iPTH fell to less than 100 pg/mL, or the Ca × P product was greater than 75 within any 2 week period, or serum calcium became greater than 11.5 mg/dL at any time.

Patients treated with Zemplar™ achieved a mean iPTH reduction of 30% within 6 weeks. In these studies, there was no significant difference in the incidence of hypercalcemia or hyperphosphatemia between Zemplar™ and placebo-treated patients. The results from these studies are as follows:

[See table above]

A long-term, open-label safety study of 164 CRF patients (mean dose of 7.5 mcg three times per week), demonstrated that mean serum Ca, P, and Ca × P remained within clinically appropriate ranges with PTH reduction (mean decrease of 319 pg/mL at 13 months).



INDICATIONS AND USAGE

Zemplar™ is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. Studies in patients with chronic renal failure show that Zemplar™ suppresses PTH levels with no significant difference in the incidence of hypercalcemia or hyperphosphatemia when compared to placebo. However, the serum phosphorus, calcium and calcium × phosphorus product (Ca × P) may increase when Zemplar™ is administered.

	Group (No. of Pts.)	Baseline Mean (Range)	Mean (SE) Change From Baseline to Final Evaluation
PTH (pg/mL)	Zemplar™ (n=40)	783 (291–2076)	−379 (43.7)
	placebo (n=38)	745 (320–1671)	−69.6 (44.8)
Alkaline Phosphatase (U/L)	Zemplar™ (n=31)	150 (40–600)	−41.5 (10.6)
	placebo (n=34)	169 (56–911)	+2.6 (10.1)
Calcium (mg/dL)	Zemplar™ (n=40)	9.3 (7.2–10.4)	+0.47 (0.1)
	placebo (n=38)	9.1 (7.8–10.7)	+0.02 (0.1)
Phosphorus (mg/dL)	Zemplar™ (n=40)	5.8 (3.7–10.2)	+0.47 (0.3)
	placebo (n=38)	6.0 (2.8–8.8)	−0.47 (0.3)
Calcium × Phosphorus Product	Zemplar™ (n=40)	54 (32–106)	+7.9 (2.2)
	placebo (n=38)	54 (26–77)	−3.9 (2.3)

CONTRAINDICATIONS

Zemplar™ should not be given to patients with evidence of vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product (see **PRECAUTIONS, General**).

WARNINGS

Acute overdose of Zemplar™ may cause hypercalcemia, and require emergency attention. During dose adjustment, serum calcium and phosphorus levels should be monitored closely (e.g., twice weekly). If clinically significant hypercalcemia develops, the dose should be reduced or interrupted. Chronic administration of Zemplar™ may place patients at risk of hypercalcemia, elevated Ca × P product, and metastatic calcification. Signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

Early

Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, and metallic taste.

Late

Anorexia, weight loss, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, hypercholesterolemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, somnolence, death, and rarely, overt psychosis.

Treatment of patients with clinically significant hypercalcemia consists of immediate dose reduction or interruption of Zemplar™ therapy and includes a low calcium diet, withdrawal of calcium supplements, patient mobilization, attention to fluid and electrolyte imbalances, assessment of electrocardiographic abnormalities (critical in patients receiving digitalis), and hemodialysis or peritoneal dialysis against a calcium-free dialysate, as warranted. Serum calcium levels should be monitored frequently until normocalcemia ensues.

Phosphate or vitamin D-related compounds should not be taken concomitantly with Zemplar™.

PRECAUTIONS

General: Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with Zemplar™. Adynamic bone lesions may develop if PTH levels are suppressed to abnormal levels.

Information for the Patient: The patient should be instructed that, to ensure effectiveness of Zemplar™ therapy, it is important to adhere to a dietary regimen of calcium supplementation and phosphorus restriction. Appropriate types of phosphate-binding compounds may be needed to control serum phosphorus levels in patients with chronic renal failure (CRF), but excessive use of aluminum containing compounds should be avoided. Patients should also be carefully informed about the symptoms of elevated calcium.

Essential Laboratory Tests: During the initial phase of medication, serum calcium and phosphorus should be determined frequently (e.g., twice weekly). Once dosage has been established, serum calcium and phosphorus should be measured at least monthly. Measurements of serum or plasma PTH are recommended every 3 months. An intact PTH (iPTH) assay is recommended for reliable detection of biologically active PTH in patients with CRF. During dose adjustment of Zemplar™, laboratory tests may be required more frequently.

Drug Interactions: Specific interaction studies were not performed. Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with Zemplar™.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of paricalcitol have not been completed. Paricalcitol did not exhibit genetic toxicity *in vitro* with or without metabolic activation in the microbial mutagenesis assay (Ames Assay), mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell chromosomal aberration assay. There was also no evidence of genetic toxicity in an *in vivo* mouse micronucleus assay. Zemplar™ had no effect on fertility (male or female) in rats at intravenous doses up to 20 mcg/kg/dose [equivalent to 13 times the highest recommended human dose (0.24 mcg/kg) based on surface area, mg/m^2].

Pregnancy: *Pregnancy Category C.* Paricalcitol has been shown to cause minimal decreases in fetal viability (5%) when administered daily to rabbits at a dose 0.5 times the 0.24 mcg/kg human dose (based on surface area, mg/m^2) and when administered to rats at a dose 2 times the 0.24 mcg/kg human dose (based on plasma levels of exposure). At the highest dose tested (20 mcg/kg 3 times per week in rats, 13 times the 0.24 mcg/kg human dose based on surface area), there was a significant increase of the mortality of newborn rats at doses that were maternally toxic (hypercalcemia). No other effects on offspring development were observed. Paricalcitol was not teratogenic at the doses tested.

There are no adequate and well-controlled studies in pregnant women. Zemplar™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether paricalcitol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemplar™ is administered to a nursing woman.

Pediatric Use: Safety and efficacy of Zemplar™ in pediatric patients have not been established.

Geriatric Use: Of the 40 patients receiving Zemplar™ in the three phase 3 placebo-controlled CRF studies, 10 patients were 65 years or over. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

ADVERSE REACTIONS

Zemplar™ has been evaluated for safety in clinical studies in 454 CRF patients. In four, placebo-controlled, double-blind, multicenter studies, discontinuation of therapy due to any adverse event occurred in 6.5% of 62 patients treated with Zemplar™ (dosage titrated as tolerated, see **CLINICAL PHARMACOLOGY, Clinical Studies**) and 2.0% of 51 patients treated with placebo for one to three months. Adverse events occurring with greater frequency in the Zemplar™ group at a frequency of 2% or greater, regardless of causality, are presented in the following table:

Adverse Event Incidence Rates for All Treated Patients in All Placebo-Controlled Studies

Adverse Event	Zemplar™ (n=62)%	Placebo (n=51)%
Overall	71	78
Body as a Whole		
Chills	5	0
Feeling unwell	3	0
Fever	5	2
Flu	5	4
Sepsis	5	2
Cardiovascular System		
Palpitation	3	0
Digestive System		
Dry mouth	3	2
Gastrointestinal bleeding	5	2
Nausea	13	8
Vomiting	8	4
Metabolic and Nutritional Disorders		
Edema	7	0
Nervous System		
Light-headedness	5	2
Respiratory System		
Pneumonia	5	0

A patient who reported the same medical term more than once was counted only once for that medical term.

Safety parameters (changes in mean Ca, P, Ca × P) in an open-label safety study up to 13 months in duration support the long-term safety of Zemplar™ in this patient population.

OVERDOSAGE

Overdosage of Zemplar™ may lead to hypercalcemia (see **WARNINGS**).

DOSAGE AND ADMINISTRATION

The currently accepted target range for iPTH levels in CRF patients is no more than 1.5 to 3 times the non-uremic upper limit of normal.

The recommended initial dose of Zemplar™ is 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7 mcg) administered as a bolus dose no more frequently than every other day at any time during dialysis. Doses as high as 0.24 mcg/kg (16.8 mcg) have been safely administered.

If a satisfactory response is not observed, the dose may be increased by 2 to 4 mcg at 2- to 4-week intervals. During any dose adjustment period, serum calcium and phosphorus levels should be monitored more frequently, and if an elevated calcium level or a Ca × P product greater than 75 is noted, the drug dosage should be immediately reduced or interrupted until these parameters are normalized. Then, Zemplar™ should be reinitiated at a lower dose. Doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, incremental dosing must be individualized

The following table is a suggested approach in dose titration:

Suggested Dosing Guidelines

PTH Level	Zemplar™ Dose
the same or increasing	increase
decreasing by <30%	increase
decreasing by >30%, <60%	maintain
decreasing by >60%	decrease
one and one-half to three times upper limit of normal	maintain

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Discard unused portion.

HOW SUPPLIED

Zemplar™ (paricalcitol injection) 5 mcg/mL is supplied as 1 and 2 mL single-dose Fliptop Vials.

List No.	Volume/ Container	Concentration	Total Content
1658	1 mL/Fliptop Vial	5 mcg/mL	5 mcg
1658	2 mL/Fliptop Vial	5 mcg/mL	10 mcg

Store at 25°C (77°F). Excursions permitted to 15°–30°C (59°–86°F)

U.S. patents: 5,246,925; 5,587,497

58-6026-R3-Rev February 2000

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

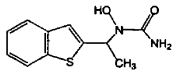
ZYFLO® FILMTAB® ℞

[zī-flo]

(zileuton tablets)

DESCRIPTION

Zileuton is an orally active inhibitor of 5-lipoxygenase, the enzyme that catalyzes the formation of leukotrienes from arachidonic acid. Zileuton has the chemical name (±)-1-(1-Benzo[b]thien-2-ylethyl)-1-hydroxyurea and the following chemical structure



Zileuton has the molecular formula $C_{11}H_{12}N_2O_2S$ and a molecular weight of 236.29. It is a racemic mixture (50:50) of R(+) and S(-) enantiomers. Zileuton is a practically odorless, white, crystalline powder that is soluble in methanol and ethanol, slightly soluble in acetonitrile, and practically insoluble in water and hexane. The melting point ranges from 144.2°C to 145.2°C. ZYFLO tablets for oral administration is supplied in one dosage strength containing 600 mg of zileuton.

Inactive Ingredients: crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, propylene glycol, sodium starch glycolate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Zileuton is a specific inhibitor of 5-lipoxygenase and thus inhibits leukotriene (LTB_4, LTC_4, LTD_4, and LTE_4) formation. Both the R(+) and S(-) enantiomers are pharmacologically active as 5-lipoxygenase inhibitors in *in vitro* systems. Leukotrienes are substances that induce numerous biological effects including augmentation of neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, increased capillary permeability, and smooth muscle contraction. These effects contribute to inflammation, edema, mucus secretion, and bronchoconstriction in the airways of asthmatic patients. Sulfido-peptide leukotrienes (LTC_4, LTD_4, LTE_4), also known as the slow-releasing substances of anaphylaxis) and LTB_4, a chemoattractant for neutrophils and eosinophils, can be measured in a number of biological fluids including bronchoalveolar lavage fluid (BALF) from asthmatic patients.

Zileuton is an orally active inhibitor of *ex vivo* LTB_4 formation in several species, including dogs, monkeys, rats, sheep, and rabbits. Zileuton inhibits arachidonic acid-induced ear edema in mice, neutrophil migration in mice in response to polyacrylamide gel, and eosinophil migration into the lungs of antigen-challenged sheep.

Zileuton inhibits leukotriene-dependent smooth muscle contractions *in vitro* in guinea pig and human airways. The compound inhibits leukotriene-dependent bronchospasm in antigen and arachidonic acid-challenged guinea pigs. In antigen-challenged sheep, zileuton inhibits late-phase bronchoconstriction and airway hyperreactivity. In humans, pretreatment with zileuton attenuated bronchoconstriction caused by cold air challenge in patients with asthma.

PHARMACOKINETICS

Zileuton is rapidly absorbed upon oral administration with a mean time to peak plasma concentration (T_{max}) of 1.7 hours and a mean peak level (C_{max}) of 4.98 µg/mL. The absolute bioavailability of ZYFLO is unknown. Systemic exposure (mean AUC) following 600 mg ZYFLO administration is 19.2 µg hr/mL. Plasma concentrations of zileuton are proportional to dose, and steady-state levels are predictable from single-dose pharmacokinetic data. Administration of ZYFLO with food resulted in a small but statistically significant increase (27%) in zileuton C_{max} without significant changes in the extent of absorption (AUC) or T_{max}. Therefore, ZYFLO can be administered with or without food (see **DOSAGE AND ADMINISTRATION**).

The apparent volume of distribution (V/F) of zileuton is approximately 1.2 L/kg. Zileuton is 93% bound to plasma proteins, primarily to albumin, with minor binding to α1-acid glycoprotein.

Elimination of zileuton is predominantly via metabolism with a mean terminal half-life of 2.5 hours. Apparent oral clearance of zileuton is 7.0 mL/min/kg. ZYFLO activity is primarily due to the parent drug. Studies with radiolabeled drug demonstrated that orally administered zileuton is well absorbed into the systemic circulation with 94.5% and 2.2% of the radiolabeled dose recovered in urine and feces, respectively. Several zileuton metabolites have been identified in human plasma and urine. These include two diastereomeric O-glucuronide conjugates (major metabolites) and an N-dehydroxylated metabolite of zileuton. The urinary excretion of the inactive N-dehydroxylated metabolite and unchanged zileuton each accounted for less than 0.5% of the dose. *In vitro* studies utilizing human liver microsomes have shown that zileuton and its N-dehydroxylated metabolite can be oxidatively metabolized by the cytochrome P450 isoenzymes 1A2, 2C9 and 3A4 (CYP1A2, CYP2C9 and CYP3A4).

Special populations:

Effect of age: Zileuton pharmacokinetics were similar in healthy elderly subjects (>65 years) compared to healthy younger adults (18 to 40 years).

Effect of gender: Across several studies, no significant gender effects were observed on the pharmacokinetics of zileuton.

Renal insufficiency: The pharmacokinetics of zileuton were similar in healthy subjects and in subjects with mild, moderate, and severe renal insufficiency. In subjects with renal failure requiring hemodialysis, zileuton pharmacokinetics were not altered by hemodialysis and a very small percentage of the administered zileuton dose (<0.5%) was removed by hemodialysis. Hence, dosing adjustment in patients with renal dysfunction or undergoing hemodialysis is not necessary.

Hepatic insufficiency: ZYFLO is contraindicated in patients with active liver disease (see **CONTRAINDICATIONS** and **PRECAUTIONS, Hepatic**).

CLINICAL STUDIES

Two double-blind, parallel, placebo-controlled, multi-center studies have established the efficacy of ZYFLO in the treatment of asthma. Three hundred seventy-three (373) patients were enrolled in the 6-month, double-blind phase of Study 1, and 401 patients were enrolled in the 3-month double-blind phase of Study 2. In these studies, the patients were mild-to-moderate asthmatics who had a mean baseline FEV_1 of approximately 2.3 liters and who used inhaled beta-agonists as needed, the mean being approximately 6 puffs of albuterol per day from a metered-dose inhaler. In each study, patients were randomized to receive either ZYFLO 400 mg four times daily, ZYFLO 600 mg four times daily, or placebo. Only the ZYFLO 600 mg four times daily dosage regimen was shown to be efficacious by demonstrating statistically significant improvement across several parameters.

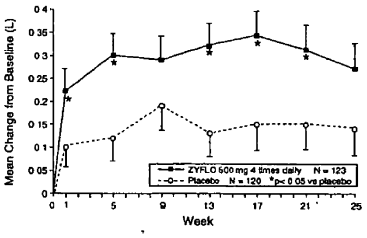
Efficacy endpoints measured in Study 1 are shown in Table 1 below as mean change from baseline to the end of the study (six months). Statistically significant differences from placebo at the $p<0.05$ level are indicated by an asterisk(*). Similar results were observed after three months in Study 2.

Table 1
MEAN CHANGE FROM BASELINE TO END OF STUDY
(Six-Month Study)

Efficacy Endpoint	ZYFLO 600 mg 4 times/ day	Placebo
Trough FEV_1(L)	0.27	0.14
AM PEFR (L/min)	30.60*	5.04
PM PEFR (L/min)	24.59*	7.98
β-Agonist Use (puffs/day)	-1.77*	-0.22
Daily Symptom Score (0–3 Scale)	-0.49*	-0.28
Nocturnal Symptom Score (0–3 Scale)	-0.29*	-0.04

Figure 1 shows the mean effect of ZYFLO versus placebo for the primary efficacy variable, trough FEV_1, over the course of Study 1.

Figure 1
Mean Change From Baseline in Trough FEV_1 (L)



Of all the patients in Study 1 and Study 2, 7.0% of those administered ZYFLO 600 mg four times daily required systemic corticosteroid therapy for exacerbation of asthma, whereas 18.7% of the placebo group required corticosteroid treatment. This difference was statistically significant.

In these trials, there was a statistically significant improvement from baseline in FEV_1, which occurred 2 hours after initial administration of ZYFLO. This mean increase was approximately 0.10 L greater than that in placebo-treated patients.

These studies evaluated patients receiving as-needed inhaled beta-agonist as their only asthma therapy. In this patient population, post-hoc analyses suggested that individuals with lower FEV_1 values at baseline showed a greater improvement.

The role of ZYFLO in the management of patients with more severe asthma, patients receiving anti-asthma therapy other than as-needed, inhaled beta-agonists, or patients receiving it as an oral or inhaled corticosteroid-sparing agent remains to be fully characterized.

INDICATIONS AND USAGE

ZYFLO is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

CONTRAINDICATIONS

ZYFLO tablets are contraindicated in patients with:

- Active liver disease or transaminase elevations greater than or equal to three times the upper limit of normal (≥3×ULN) (see **PRECAUTIONS, Hepatic**).
- Hypersensitivity to zileuton or any of its inactive ingredients

WARNINGS

ZYFLO is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus. Therapy with ZYFLO can be continued during acute exacerbations of asthma.

Co-administration of ZYFLO and theophylline results in, on average, an approximate doubling of serum theophylline concentrations. Theophylline dosage in these patients should be reduced and serum theophylline concentrations monitored closely (see **PRECAUTIONS, Drug Interactions**).

Co-administration of ZYFLO and warfarin results in a clinically significant increase in prothrombin time (PT). Patients on oral warfarin therapy and ZYFLO should have their prothrombin times monitored closely and anticoagulant dose adjusted accordingly (see **PRECAUTIONS, Drug Interactions**).

Co-administration of ZYFLO and propranolol results in doubling of propranolol AUC and consequent increased

Continued on next page

Adverse Events Reported by ≥2% of Hectorol treated patients and more frequently than placebo during the double-blind phase of two Clinical Studies

Adverse Event	Hectorol (n=61) %	Placebo (n=61) %
Body as a Whole		
Abscess	3.3	0.0
Headache	27.9	18.0
Malaise	27.9	19.7
Cardiovascular System		
Bradycardia	6.6	4.9
Digestive System		
Anorexia	4.9	3.3
Constipation	3.3	3.3
Dyspepsia	4.9	1.6
Nausea/Vomiting	21.3	19.7
Musculo-Skeletal System		
Arthralgia	4.9	0.0
Metabolic and Nutritional		
Edema	34.4	21.3
Weight increase	4.9	0.0
Nervous System		
Dizziness	11.5	9.8
Sleep disorder	3.3	0.0
Respiratory System		
Dyspnea	11.5	6.6
Skin		
Pruritus	8.2	6.6

A patient who reported the same medical term more than once was counted only once for that medical term.

Initial Dosing

iPTH Level	Hectorol Dose
> 400 pg/mL	10.0 mcg three times per week at dialysis

Dose Titration

iPTH Level	Hectorol Dose
Decreased by < 50% and above 300 pg/mL	Increase by 2.5 mcg at eight-week intervals as necessary
150–300 pg/mL	Maintain
< 100 pg/mL	Suspend for one week, then resume at a dose that is at least 2.5 mcg lower

in human milk and because of the potential for serious adverse reactions in nursing infants from doxercalciferol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy of Hectorol in pediatric patients have not been established.

Geriatric Use

Of the 138 patients treated with Hectorol Capsules in two Phase 3 clinical studies, 30 patients were 65 years or over. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

Hepatic Insufficiency

Since patients with hepatic insufficiency may not metabolize Hectorol appropriately, the drug should be used with caution in patients with impaired hepatic function. More frequent monitoring of iPTH, calcium, and phosphorus levels should be done in such individuals.

ADVERSE REACTIONS

Hectorol has been evaluated for safety in clinical studies in 165 patients with chronic renal disease on hemodialysis. In two placebo-controlled, double-blind, multicenter studies, discontinuation of therapy due to any adverse event occurred in 2.9% of 138 patients treated with Hectorol for four to six months (dosage titrated to achieve target iPTH levels, see **CLINICAL PHARMACOLOGY/Clinical Studies**) and in 3.3% of 61 patients treated with placebo for two months. Adverse events occurring in the Hectorol group at a frequency of 2% or greater and more frequently than in the placebo group are presented in the following table:

[See first table above]

Potential adverse effects of Hectorol are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

Early

Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, and metallic taste

Late

Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, elevated serum aspartate transaminase (AST) and alanine transminase (ALT), ectopic calcification, hypertension, cardiac arrhythmias, and, rarely, overt psychosis.

OVERDOSAGE

Administration of Hectorol to patients in excess doses can cause hypercalcemia, hypercalciuria, hyperphosphatemia, and oversuppression of PTH secretion leading in certain cases to adynamic bone disease. High intake of calcium and phosphate concomitant with Hectorol may lead to similar abnormalities. High levels of calcium in the dialysate bath may contribute to hypercalcemia.

Treatment of Hypercalcemia and Overdosage

General treatment of hypercalcemia (greater than 1 mg/dL above the upper limit of the normal range) consists of immediate suspension of Hectorol therapy, institution of a low calcium diet, and withdrawal of calcium supplements. Serum calcium levels should be determined at least weekly until normocalcemia ensues. Hypercalcemia usually resolves in 2 to 7 days. When serum calcium levels have returned to within-normal limits, Hectorol therapy may be reinstituted at a dose that is at least 2.5 mcg lower than prior therapy. Serum calcium levels should be obtained weekly after all dosage changes and during subsequent dosage titration. Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a reduced calcium or calcium-free dialysate.

Treatment of Accidental Overdosage of Doxercalciferol

The treatment of acute accidental overdosage of Hectorol should consist of general supportive measures. If drug ingestion is discovered within a relatively short time (10 minutes), induction of emesis or gastric lavage may be of benefit in preventing further absorption. If drug ingestion is discovered later than 10 minutes post-ingestion, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion, and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and institution of a low calcium diet are also indicated in accidental overdosage. If persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives that may be considered. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce diuresis. Also, one may consider dialysis against a calcium-free dialysate.

DOSAGE AND ADMINISTRATION

Adult Administration:

The optimal dose of Hectorol must be carefully determined for each patient.

The recommended initial dose of Hectorol is 10.0 mcg administered three times weekly at dialysis (approximately every other day). The initial dose should be adjusted, as needed, in order to lower blood iPTH into the range of 150 to 300 pg/mL. The dose may be increased at 8-week intervals by 2.5 mcg if iPTH is not lowered by 50% and fails to reach the target range. The maximum recommended dose of Hectorol is 20 mcg administered three times a week at dialysis for a total of 60 mcg per week. Drug administration should be suspended if iPTH falls below 100 pg/mL and restarted one week later at a dose that is at least 2.5 mcg lower than the last administered dose. During titration, iPTH, serum calcium, and serum phosphorus levels should be obtained weekly. If hypercalcemia, hyperphosphatemia, or a serum calcium times serum phosphorus product greater than 70 is noted, the drug should be immediately suspended until these parameters are appropriately lowered. Then, the drug should be restarted at a dose that is at least 2.5 mcg lower.

Dosing must be individualized and based on iPTH levels with monitoring of serum calcium and serum phosphorus levels. The following is a suggested approach in dose titration:

[See second table at left]

HOW SUPPLIED

NDC 64894-825-50

2.5 mcg doxercalciferol in soft gelatin, sunshine yellow, oval capsules, imprinted **BCI**; bottles of 50

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Manufactured by R.P. Scherer North America for
Bone Care International, Inc., Middleton, WI 53562
888-389-4242

PI-001-00 11/00

Shown in Product Identification Guide, page 309

HECTOROL® INJECTION ℞

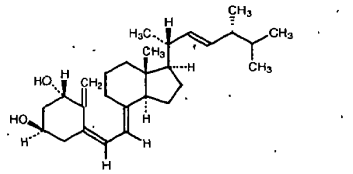
[heck'-tŏrŏl]

(Doxercalciferol)

DESCRIPTION

Doxercalciferol, the active ingredient in Hectorol, is a synthetic vitamin D analog that undergoes metabolic activation *in vivo* to form 1α,25-dihydroxyvitamin D_2 (1α,25-$(OH)_2D_2$), a naturally occurring, biologically active form of vitamin D_2. Hectorol is available as a sterile, clear, colorless, aqueous solution for intravenous injection. Each milliliter (mL) of solution contains doxercalciferol, 2 mcg; TWEEN® Polysorbate 20, 4 mg; sodium chloride, 1.5 mg; sodium ascorbate, 10 mg, sodium phosphate, dibasic 7.6 mg; sodium phosphate, monobasic 1.8 mg; and disodium edetate, 1.1 mg.

Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 412.66 and a molecular formula of $C_{28}H_{44}O_2$. It is soluble in oils and organic solvents, but is relatively insoluble in water. Chemically, doxercalciferol is (1α,3β,5Z,7E,22E)-9,10-secoergosta-5,7,10(19) 22-tetraen-1,3-diol and has the following structural formula



Other names frequently used for doxercalciferol are 1α-hydroxyvitamin D_2, 1α-OH-D_2, and 1α-hydroxyergocalciferol.

CLINICAL PHARMACOLOGY

Vitamin D levels in humans depend on two sources: (1) exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol in the skin to vitamin D_3 (cholecalciferol) and (2) dietary intake of either vitamin D_2 (ergocalciferol) or vitamin D_3. Vitamin D_2 and vitamin D_3 must be metabolically activated in the liver and kidney before becoming fully active on target tissues. The initial step in the activation process is the introduction of an hydroxyl group in the side chain at C-25 by an hepatic enzyme, CYP 27 (a vitamin D-25-hydroxylase). The products of this reaction are 25-$(OH)D_2$ and 25-$(OH)D_3$, respectively. Further hydroxylation of these metabolites occurs in the mitochondria of kidney tissue, catalyzed by renal 25-hydroxyvitamin D-1-α-hydroxylase to produce 1α,25-$(OH)_2D_2$, the primary biologically active form of vitamin D_2, and 1α,25-$(OH)_2D_3$ (calcitriol), the biologically active form of vitamin D_3.

Mechanism of Action

Calcitriol (1α,25-$(OH)_2D_3$) and 1α,25-$(OH)_2D_2$ regulate blood calcium at levels required for essential body functions. Specifically, the biologically active vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidney and, in conjunction with parathyroid hormone (PTH), the mobilization of calcium from the skeleton. They act directly on bone cells (osteoblasts) to stimulate skeletal growth, and on the parathyroid glands to suppress PTH synthesis and secretion

Continued on next page

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