PDR® 52 EDITION 1998

PHYSICIANS' DESK REFERENCE®

Medical Consultant
Ronald Arky, MD, Charles S. Davidson Professor of Medicine and Master, Francis Weld Peabody Society, Harvard Medical School

Vice President of Directory Services: Stephen B. Greenberg

Product Manager: Mark A. Friedman
National Sales Manager: Dikran N. Barsamian
National Account Manager, Customized Projects: Anthony Sorce
Senior Account Manager: Donald V. Bruccoleri
Account Managers:
Marion Gray, RPh
Lawrence C. Keary
Jeffrey F. Pfohl
Stephen M. Silverberg
Suzanne E. Yarrow
Director of Trade and Direct Marketing Sales: Robin B. Bartlett
National Sales Manager, Trade Group: Bill Gaffney
Promotion Manager: Donna R. Lynn
Director, Professional Support Services: Mukesh Mehta, RPh
Senior Drug Information Specialist: Thomas Fleming, RPh
Drug Information Specialist: Maria Deutsch, MS, RPh, CDE
Editor, Special Projects: David W. Sifton

Vice President of Production: David A. Pitler
Director of Print Purchasing: Marjorie A. Duffy
Director of Database Services: Lynne Handler
Director of Production: Carrie Williams
Manager of Production: Kimberly Hiller-Vivas
Senior Production Coordinators: Amy B. Brooks, Dawn B. McCall
Production Coordinator: Mary Ellen R. Breun
Index/Format Manager: Jeffrey D. Schaefer
Senior Format Editor: Gregory J. Westley
Assistant Index Editor: Johanna M. Mazur
Art Associate: Joan K. Akerlind
Electronic Publishing Coordinator: Joanne M. Pearson
Senior Digital Imaging Coordinator: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Electronic Publishing Designer: Robert K. Grossman
Fulfillment Managers: Stephanie DeNardi, Stephen Schweikhart

Officers of Medical Economics Company: *President and Chief Executive Officer:* Curtis B. Allen; *Vice President, Human Resources:* Pamela M. Bilash; Vice President and Chief Information Officer: Steven M. Bressler; *Vice President, Finance, and Chief Financial Officer:* Thomas W. Ehardt; *Executive Vice President and Chief Operating Officer:* Rick Noble; *Executive Vice President, Magazine Publishing:* Thomas F. Rice; *Senior Vice President, Operations:* John R. Ware

Printed on recycled paper

ISBN: 1-56363-251-9

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No studies have been performed to evaluate carcinogenic or mutagenic potential of Diucardin or the potential of Diucardin to impair fertility.
PREGNANCY
Teratogenic Effects—Pregnancy Category C
Animal reproduction studies have not been conducted with Diucardin. It is also not known whether Diucardin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Diucardin should be given to a pregnant woman only if clearly needed.
Nonteratogenic Effects
Fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.
NURSING MOTHERS
Thiazides appear in breast milk. If use of the drug is deemed essential, the patient may consider stopping nursing.
PEDIATRIC USE
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reactions have been observed, but there is not enough systematic collection of data to support an estimate of their frequency.
GASTROINTESTINAL SYSTEMS
Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis.
CENTRAL NERVOUS SYSTEM
Dizziness, vertigo, paresthesias, headache, xanthopsia.
HEMATOLOGIC
Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia.
CARDIOVASCULAR
Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics).
DERMATOLOGIC—HYPERSENSITIVITY
Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions.
OTHER
Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision.
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE

SIGNS AND SYMPTOMS
Diuresis, lethargy progressing to coma, with minimal cardiorespiratory depression and with or without significant serum electrolyte changes or dehydration; GI irritation; hypermotility; transient elevation in BUN level.
TREATMENT
Empty stomach by gastric lavage, taking care to avoid aspiration. Monitor serum electrolyte levels and renal function, and institute supportive measures, as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function. Treat GI effects symptomatically.

DOSAGE AND ADMINISTRATION

The average adult diuretic dose is 25 to 200 mg per day. The average adult antihypertensive dose is 50 to 100 mg per day. Therapy should be individualized according to patient response. This therapy should be titrated to gain maximal response as well as the minimal dose possible to maintain that therapeutic response.

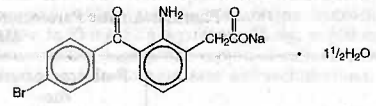
HOW SUPPLIED

Diucardin®—Each scored, white oval compressed tablet, inscribed "DIUCARDIN 50," contains 50 mg hydroflumethiazide, in bottles of 100 (NDC 0046-0702-81).
Store at room temperature (approximately 25° C)
Dispense in a well-closed container as defined in the USP
Caution: Federal law prohibits dispensing without prescription.
Manufactured by:
Ayerst Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101
Shown in Product Identification Guide, page 341

DURACT™ ℞
[dŏr 'ăkt]
bromfenac sodium capsules

DESCRIPTION

Bromfenac sodium is benzene acetic acid, 2-amino-3-(4-bromobenzyl)-, monosodium salt, sesquihydrate. It is an



dium is a non-hygroscopic, yellow to orange crystalline powder. It is soluble in water, propylene glycol, PEG-400, and glycerin. DURACT (bromfenac sodium capsule) contains 28.76 mg of bromfenac sodium sesquihydrate, equivalent to 25 mg of bromfenac base and 1.73 mg of sodium, for oral administration.
The inactive ingredients are: gelatin, lactose, magnesium stearate, silicon dioxide, titanium dioxide, and FD&C Blue #1, FD&C Red #40, D&C Yellow #10.

CLINICAL PHARMACOLOGY

DURACT is considered a peripherally acting analgesic that belongs to the nonsteroidal anti-inflammatory drug (NSAID) class.
PHARMACODYNAMICS
Following single doses of 25 and 50 mg of DURACT, onset on analgesia was demonstrable in various pain models within 30 minutes, reaching peak effects between 2 and 3 hours, and median duration of analgesia of 6 to 7 hours (see **Clinical Studies**).
PHARMACOKINETICS
The analgesic activity of bromfenac is due to the parent drug. Studies with radiolabeled drug have demonstrated that bromfenac administered orally as DURACT is absorbed into systemic circulation with 80% of the radiolabel recovered in the urine. The median oral-dose clearance of bromfenac is 0.08 L/h/kg and the volume of distribution is 0.15 L/kg. Elimination of bromfenac is due to hepatic metabolism with subsequent renal elimination of metabolites; no unchanged drug has been found in the urine. The terminal elimination half-life is approximately 1.3 hours. The observed plasma half-life of bromfenac does not correlate with the duration of action. Concomitant ingestion of food causes a significant decrease in bromfenac bioavailability (see *Food Effects*).
Pharmacokinetic parameters for bromfenac are shown in the table below.
[See table at top of next page]
Absorption: Bromfenac is absorbed after oral administration with peak plasma levels occurring approximately 45 minutes after dosing. The absolute bioavailability of DURACT is approximately 67% in humans. The pharmacokinetics of bromfenac are best described by a one-compartment model with first-order absorption. Dose proportionality, based on AUC (area under the plasma-concentration time curve), has been demonstrated between single doses from 5 to 100 mg. There was no drug accumulation after administration of multiple doses using an every 8 or every 12 hour dosing regimen.
Antacid Effects: Following the concomitant administration of an aluminum hydroxide containing antacid with bromfenac, peak plasma levels of bromfenac were reduced by 36%. There was no effect on the overall extent of bromfenac absorption.
Food Effects: The concomitant administration of a high-fat meal with bromfenac causes a 75% reduction in peak plasma concentrations and a 60% reduction in total AUC. *In vivo* pharmacokinetic studies have demonstrated that the absorption of bromfenac is greatly reduced if the drug is administered with, or up to $3\frac{1}{2}$ hours after, a high fat standardized meal (see **Clinical Studies**).
Distribution: Bromfenac is more than 99% bound to human plasma proteins. The unbound fraction is independent of concentration over the dose range studied.
Metabolism: After the ingestion of [^{14}C] bromfenac sodium, virtually all of the radioactivity in plasma is accounted for as unchanged drug. In the urine, a cyclic amide metabolite and four glucuronide conjugates of aglycone metabolites account for most of the radioactivity recovered in the urine. The precise iso-enzyme of cytochrome P-450 involved in the metabolism of bromfenac has not been identified (see **Precautions**—DRUG INTERACTIONS). Bromfenac has no effect on the pharmacokinetics of digoxin, glyburide, methotrexate, or phenytoin.
Elimination: In the same radiolabeled study referred to above, an average of 80% of the radioactivity has been recovered in the urine within 24 hours. Neither unchanged bromfenac nor bromfenac conjugates have been recovered from urine.
Special Populations: A population pharmacokinetic analysis of the data from patients receiving bromfenac showed that the variability between patients was not linked to sex, weight, or calculated creatinine clearance. The observations in clinical trials were in agreement with those seen in healthy volunteers, and suggest that no dosage adjustment is required based on any of these patient characteristics.
Elderly: In a study with 24 subjects greater than 65 years half-life increased from 1.3 to 2.8 hrs (see Table). In these subjects, an increased time between doses should be considered.
Hepatic Impairment: While the disposition of total and unbound bromfenac was not altered in patients with mild to moderate hepatic disease, the observed oral clearance was reduced by 40%. This reduction in clearance caused a prolongation of the observed median plasma half-life to 3.1 hrs (vs. 2 hrs in the appropriate control sample).
Renal Impairment: In a study of the effects of mild to severe renal impairment (CrCl < 60 mL/min), no significant differences were seen in the disposition of total and unbound bromfenac. In subjects undergoing hemodialysis, unbound bromfenac clearance was not altered. No dosage adjustment of DURACT is required in patients with mild to severe renal impairment; however, DURACT should be used with caution in such patients because NSAIDs may further decrease renal function in some patients with preexisting impairment.

CLINICAL STUDIES

Clinical trials for analgesic efficacy were conducted in *fasted* patients with moderate or severe acute pain following surgery (major abdominal, orthopedic, or oral surgery). DURACT 25 mg, given orally, was comparable to oral naproxen sodium 550 mg, and ibuprofen 400 mg. Doses of 25 mg of DURACT were superior to aspirin 650 mg. In one oral surgery study, a 25 mg dose of DURACT, given with a high fat meal, was effective but inferior to 25 mg given to fasted patients.
In repeat-dose postsurgical pain studies of acute pain, DURACT was administered every 6 to 8 hours, as needed, for up to 1 week. In these studies, DURACT was comparable to naproxen sodium (550 mg followed by 275 mg).

INDICATIONS AND USAGE

DURACT is indicated for the short-term (generally less than 10 days) management of pain. DURACT is not indicated for the treatment of such conditions as osteoarthritis or rheumatoid arthritis.

CONTRAINDICATIONS

DURACT is contraindicated in patients who have known hypersensitivity to bromfenac. DURACT should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe anaphylactic-like reactions to drugs in this class have been reported (see **Warnings**—ANAPHYLACTOID REACTIONS and **Precautions**—GENERAL PRECAUTIONS, *Pre-Existing Asthma*). Such reactions may be fatal if not treated promptly. DURACT should be avoided in patients with known chronic hepatitis.

WARNINGS

HEPATIC EFFECTS
Elevations of one or more liver tests may occur during DURACT therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient despite continued therapy. As with other NSAIDs, borderline elevations (i.e., less than 3 times the Upper Limit of Normal [ULN]) or greater elevations of transaminases occurred in clinical trials (n=926) at some time during treatment in approximately 15% of DURACT-treated patients. Elevations to more than 3 times the ULN of AST (SGOT) or ALT (SGPT) occurred in 2.7% of these patients at some time during DURACT treatment, but the incidence of such elevations during short-term therapy was less than 0.4%. Marked elevations (i.e., more than 8 times the ULN) occurred in 0.4% of patients in longer term trials. The enzyme elevations seen in clinical trials have been reversible after discontinuation of therapy (see **Adverse Reactions**).
Short-term management of pain should generally be less than ten days duration. Because hepatotoxicity may develop without a prodrome of distinguishing symptoms, if a physician chooses to administer DURACT for a longer duration, the patient's transaminases, particularly ALT, should be monitored for evidence of hepatotoxicity after 4 weeks. DURACT should be avoided in patients with known severe hepatic disease and should be used with caution in patients with less severe pre-existing liver impairment (see **Precautions**).
GASTROINTESTINAL (GI) EFFECTS—RISK OF GI ULCERATION, BLEEDING, AND PERFORATION
Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper GI problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Only one in five patients, who develop a serious upper

Anaphylactoid reactions may occur in patients without known prior exposure to bromfenac. DURACT should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Fatal reactions to NSAIDs have been reported in such patients (see **Contraindications** and **Precautions**—GENERAL PRECAUTIONS, *Pre-Existing Asthma*). Emergency help should be sought when an anaphylactoid reaction occurs.

PREGNANCY

As with other NSAIDs, DURACT should be avoided in late pregnancy, because it may cause premature closure of the ductus arteriosus and delay parturition (see **Precautions**—PREGNANCY).

PRECAUTIONS

GENERAL PRECAUTIONS

Renal Effects

Renal toxicity associated with NSAIDs is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation.

Patients at greatest risk of this reaction are those with volume depletion, impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Pre-existing Asthma

About 10% of patients with asthma have aspirin-sensitive asthma. The use of aspirin in patients suffering from aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported, DURACT should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

Hematological Effects

All drugs that inhibit the biosynthesis of prostaglandin may interfere to some extent with platelet function and vascular responses to bleeding. DURACT inhibits platelet aggregation and may prolong bleeding time. In contrast to aspirin's prolonged effect on platelets, the inhibition of platelet function by bromfenac sodium disappears within 24 hours. DURACT does not affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving DURACT who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Anemia is sometimes seen in patients receiving NSAIDs, including DURACT™. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis.

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking DURACT. Therefore, as with other NSAIDs, DURACT should be used with caution in patients with fluid retention, hypertension, or heart failure.

INFORMATION FOR PATIENTS

Analgesic treatment with DURACT should be guided by the patient's response. The individual response to DURACT can be determined when the patient perceives a return of pain that necessitates the taking of the next dose. The time between the first and second dose should be a guide to subsequent doses, without exceeding the recommended total daily dose of 150 mg. Patients should take the lowest effective total daily dose to minimize the potential for adverse events.

(see **Clinical Pharmacology**—PHARMACOKINETICS, *Food Effects*).

DURACT, like other NSAIDs, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there may be serious side effects, such as drug-induced hepatitis and gastrointestinal bleeding, that may result in hospitalization and even fatal outcomes. Patients should be instructed to report any flu-like symptoms (that may be an early signal of hepatic damage), as well as signs and symptoms of gastrointestinal bleeding.

As with other NSAIDs, DURACT should be avoided in late pregnancy, because it may cause premature closure of the ductus arteriosus and delay parturition.

LABORATORY TESTS

Elevations of one or more liver tests may occur during DURACT therapy (see **Warnings**—HEPATIC EFFECTS).

DRUG INTERACTIONS

Cimetidine

The concomitant administration of cimetidine caused a moderate increase in bromfenac concentrations. The clearance of bromfenac was decreased by 17% in patients taking cimetidine, but bromfenac has no effect on the pharmacokinetics of cimetidine.

Lithium

The interaction between lithium and bromfenac has not been studied. However, other NSAIDs are known to cause an increase in blood lithium concentrations, thus increasing the possibility of toxic events to lithium when concomitantly administered with DURACT.

Phenytoin

As with other drugs metabolized by the cytochrome P450 pathways, phenytoin reduced the plasma levels of bromfenac by about 50%. Bromfenac has no effect on the pharmacokinetics of phenytoin.

Warfarin

Coadministration of bromfenac has no effect on warfarin pharmacokinetics or its anticoagulant effect. Warfarin has no effect on the pharmacokinetics of bromfenac. Nevertheless, caution should be exercised when adding any drug that affects platelet function, such as DURACT, to patients receiving oral anticoagulants.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No carcinogenic effect of bromfenac was observed in rats given oral dosages of up to 0.60 mg/kg (3.6 mg/m^2/day), or in mice given oral dosages of up to 7.5 mg/kg (22.5 mg/m^2/day) for two years.

Bromfenac was not mutagenic in *in vitro* tests performed with *S. typhimurium*, mouse lymphoma cells and Chinese hamster ovary cells, an *in vitro* micronucleus test, and an *in vivo* unscheduled DNA synthesis assay. Bromfenac showed no impairment of fertility in male and female rats up to oral dosages of 0.9 mg/kg (5.4 mg/m^2/day).

PREGNANCY: TERATOGENIC EFFECTS: PREGNANCY CATEGORY C

No teratogenic potential was demonstrated in rats up to an oral dosage of 0.9 mg/kg (5.4 mg/m^2/day) or in rabbits up to an oral dosage of 7.5 mg/kg (82.5 mg/m^2/day). Maternal and fetal effects (reduced embryo/fetal survival) occurred at an oral dosage of 7.5 mg/kg in rabbits.

There are no adequate or well-controlled studies of DURACT in pregnant women. DURACT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Since NSAIDs are known to delay parturition or cause premature closure of the ductus arteriosus, DURACT should be avoided during late pregnancy.

LABOR AND DELIVERY

As with other NSAIDs, the effects of bromfenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on uterine contractions, DURACT may cause secondary uterine dystocia and delay parturition. In rat studies with bromfenac, as

NURSING MOTHERS

Bromfenac is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from DURACT, a decision should be made whether to discontinue nursing or to discontinue this drug, taking into account the importance of the drug to the mother.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established.

GERIATRIC POPULATION

In volunteers greater than 75 years of age, the terminal half-life of bromfenac is increased from 1.3 to 2.8 hours. The dosing interval may need to be adjusted (increased) for patients older than 75. (See **Clinical Pharmacology** and **Dosage and Administration**).

ADVERSE REACTIONS

Adverse reaction data were derived from approximately 2400 patients who received DURACT in single- and multiple-dose studies. As with other NSAIDs, the incidence of adverse drug reactions attributed to DURACT was lower in single-dose studies than the incidence associated with repeated dosing. The adverse event rates listed below refer to the incidence of treatment-emergent symptoms seen in 926 patients in those repeated-dose clinical trials that involved a course of therapy sufficient to include the recommended duration of use (see **Indications and Usage** and **Dosage and Administration**). To distinguish different rates of occurrence in clinical studies, the adverse events are listed as follows:

name of adverse event = < 3%

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

adverse event rates over 9% are in parenthesis

INCIDENCE GREATER THAN 1%

Body as a whole: Asthenia, headache*

Digestive system: Abdominal pain*, constipation, diarrhea, dyspepsia (12%), eructation, flatulence, liver enzyme elevations (< 3× upper limit of normal)*, nausea*, vomiting.

Nervous system: Dizziness*, somnolence*.

INCIDENCE LESS THAN 1%

Body as a whole: Back pain, chest pain, chills, face edema, fever, flu syndrome, generalized edema, infection, malaise.

Cardiovascular system: Arrhythmias, hemorrhage, hypertension, migraine myocardial infarction, palpitations, phlebitis, syncope, vasodilation.

Digestive system: Anorexia, colitis, dry mouth, gastritis, gastroenteritis, gastrointestinal hemorrhage, increased appetite, liver test abnormalities (≥ 3 × upper limit of normal), pancreatitis, peptic ulcer, periodontal abscess, positive fecal occult blood test, rectal disorder, stomatitis, tenesmus.

Endocrine: Glycosuria.

Hemic and lymphatic system: Anemia, ecchymosis, leukopenia.

Metabolic and nutritional: Blood urea nitrogen increased, edema, hypoglycemia, hypokalemia, hyponatremia, serum creatinine increased, thirst, weight gain, weight loss.

Musculoskeletal: Leg cramps, myalgia.

Nervous system: Abnormal dreams, amnesia, anxiety, confusion, depression, emotional lability, euphoria, hallucination, incoordination, insomnia, libido increased, nervousness, paresthesia, psychosis, tremor, twitching.

Respiratory system: Asthma, cough increased, dyspnea, epistaxis, hiccup, hyperventilation, pharyngitis, rhinitis, sinusitis.

Skin and appendages: Alopecia, pruritus, rash, seborrhea, skin infections, skin ulcer, sweating, urticaria.

Special senses: Abnormal vision, blepharitis, cataract, conjunctivitis, dry eyes, ear disorder, lacrimation, photophobia, taste perversion, tinnitus.

Urogenital: Albuminuria, breast pain, dysuria, hematuria, impotence, menstrual disorder, nocturia, oliguria, orchitis, polyuria, pyuria, uterine fibroids enlarged, urinary frequency, uterine hemorrhage, urinary incontinence, urinary tract infection.

OVERDOSAGE

No cases of DURACT overdose have been reported. Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive NSAID overdose. Hypertension, acute renal failure, and respiratory depression may occasionally occur. Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or an osmotic cathartic may be indicated in patients seen within 4 hours with symptoms or following a large overdose (5–10 times the usual dose). Dialysis is not likely to be effective for removal of bromfenac because it is more than 99% bound to plasma proteins.

DOSAGE AND ADMINISTRATION

For the short-term (generally less than 10 days) management of pain, the recommended dose of DURACT is 25 mg every 6 to 8 hours, as necessary, except when taken with high-fat food, when a 50 mg dose may be needed (see below). The total daily dose should not exceed 150 mg.

Bromfenac sodium, like other NSAIDs, shows considerable inter-individual variation in patient response, but the bioavailability of bromfenac was shown to be especially sensitive to the effect of a high-fat meal (see **Clinical Pharmacology**—PHARMACOKINETICS, *Food Effects*). The effects of light, low-fat meals on the absorption of bromfenac have not been investigated.

As with other NSAIDs, 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 DURACT, the dose and frequency of dosing should be adjusted to suit each individual patient's needs, without exceeding the maximum total daily dose recommended (150 mg).

HOW SUPPLIED

DURACT™ Capsules are available as:

25 mg of bromfenac (as bromfenac sodium), opaque light yellow body with two 300° blue bands, opaque red cap, branded "DURACT" in blue ink.

— Bottles of 100 capsules (NDC 0008-0909-01)

— Redipak® cartons each containing 10 blister strips of 10 capsules (NDC 0008-0909-03)

Store at controlled room temperature, 20° to 25°C (68° to 77°F), protected from moisture and light.

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

The appearance of these capsules is a trademark of Wyeth-Ayerst Laboratories.

Manufactured by:
Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

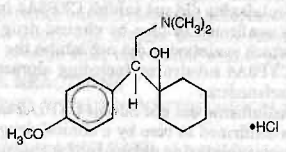
Shown in Product Identification Guide, page 341

EFFEXOR®

(venlafaxine hydrochloride)
Tablets

DESCRIPTION

Effexor (venlafaxine hydrochloride) is a structurally novel antidepressant for oral administration. It is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2HCl$. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Compressed tablets contain venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg, or 100 mg venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α-1 adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

PHARMACOKINETICS

Venlafaxine is well absorbed and extensively metabolized in the liver. O-desmethylvenlafaxine (ODV) is the only major active metabolite. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The relative bioavailability of venlafaxine from a tablet was 100% when compared to an oral solution. Food has no significant effect on the absorption of venlafaxine or on the formation of ODV.

The degree of binding of venlafaxine to human plasma is 27%±2% at concentrations ranging from 2.5 to 2215 ng/mL. The degree of ODV binding to human plasma is 30%±12% at concentrations ranging from 100 to 500 ng/mL. Protein-binding-induced drug interactions with venlafaxine are not expected.

Steady-state concentrations of both venlafaxine and ODV in plasma were attained within 3 days of multiple-dose therapy. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg total dose per day (administered on a q8h schedule). Plasma clearance, elimination half-life and steady-state volume of distribution were unaltered for both venlafaxine and ODV after multiple-dosing. Mean±SD steady-state plasma clearance of venlafaxine and ODV is 1.3±0.6 and 0.4±0.2 L/h/kg, respectively; elimination half-life is 5±2 and 11±2 hours, respectively; and steady-state volume of distribution is 7.5±3.7 L/kg and 5.7±1.8 L/kg, respectively. When equal daily doses of venlafaxine were administered as either b.i.d. or t.i.d. regimens, the drug exposure (AUC) and fluctuation in plasma levels of venlafaxine and ODV were comparable following both regimens.

Age and Gender

A pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or ODV were unaltered due to age or gender differences. Dosage adjustment based upon the age or gender of a patient is generally not necessary (see **"Dosage and Administration"**).

Liver Disease

In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic patients compared to normal subjects. ODV elimination half-life was prolonged by about 60% and clearance decreased by about 30% in cirrhotic patients compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects.

Dosage adjustment is necessary in these patients (see **"Dosage and Administration"**).

Renal Disease

In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR =10-70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, ODV elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR =10-70 mL/min) compared to normal subjects. Dosage adjustment is necessary in these patients (see **"Dosage and Administration"**).

CLINICAL TRIALS

The efficacy of Effexor (venlafaxine hydrochloride) as a treatment for depression was established in 5 placebo-controlled, short-term trials. Four of these were 6-week trials in outpatients meeting DSM-III or DSM-III-R criteria for major depression: two involving dose titration with Effexor in a range of 75 to 225 mg/day (t.i.d. schedule), the third involving fixed Effexor doses of 75, 225, and 375 mg/day (t.i.d. schedule), and the fourth involving doses of 25, 75, and 200 mg/day (b.i.d. schedule). The fifth was a 4-week study of inpatients meeting DSM-III-R criteria for major depression with melancholia whose Effexor doses were titrated in a range of 150 to 375 mg/day (t.i.d. schedule). In these 5 studies, Effexor was shown to be significantly superior to placebo on at least 2 of the following 3 measures: Hamilton Depression Rating Scale (total score), Hamilton depressed mood item, and Clinical Global Impression—Severity of Illness rating. Doses from 75 to 225 mg/day were superior to placebo in outpatient studies and a mean dose of about 350 mg/day was effective in inpatients. Data from the 2 fixed-dose outpatient studies were suggestive of a dose-response relationship in the range of 75 to 225 mg/day. There was no suggestion of increased response with doses greater than 225 mg/day.

While there were no efficacy studies focusing specifically on an elderly population, elderly patients were included among the patients studied. Overall, approximately $^2/_3$ of all patients in these trials were women. Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

Effexor (venlafaxine hydrochloride) is indicated for the treatment of depression.

The efficacy of Effexor in the treatment of depression was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III or DSM-III-R category of major depressive disorder and in a 4-week controlled trial of inpatients meeting diagnostic criteria for major depressive disorder with melancholia (see **"Clinical Pharmacology"**).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effectiveness of Effexor in long-term use, that is, for more than 4 to 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Effexor for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Effexor (venlafaxine hydrochloride) is contraindicated in patients known to be hypersensitive to it.

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **"Warnings"**).

WARNINGS

POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS

Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on Effexor, or who have recently had Effexor therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with a monoamine oxidase inhibitor, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. Therefore, it is recommended that Effexor not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Effexor