ORIGINAL CONTRIBUTION

Fusobacterial Infections

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Anaerobic, Gram-negative bacilli of the genus *Fusobacterium* have been implicated in the etiology, pathophysiology, and complications of several diseases, including periodontal diseases, Lemierre's syndrome, tropical skin ulcers, and intraamniotic infections (IAI). As part of the normal flora of the oral cavity, female genital tract, and gastrointestinal tract, fusobacteria have a number of natural entry points to cause disease. *F. nucleatum* plays a critical role in the development of periodontal diseases by acting as a microbial bridge between early and late (pathogenic) colonizers of the oral tissues. *F. necrophorum* is the causative agent of Lemierre's syndrome, a rare infection that can have devastating effects on the joints, lungs, and central nervous system. A variety of fusobacteria have been implicated in the development of tropical skin ulcers, which continue to cause significant debility in regions of the tropics. Fusobacteria have been associated with a significant proportion of preterm low birth weight infants due to IAI. Morbidity and mortality may result from IAI, and the incidence of IAI has not decreased in recent years. Typically, antimicrobial drugs provide effective treatment of fusobacterial infections, which can affect people of all age groups.

INTRODUCTION

Fusobacteria, which form part of the family *Bacteroidaceae*, are asaccharolytic obligately anaerobic, non-spore forming, Gram-negative bacilli (1,2). Historically, the production of butyric acid, rather than isobutyric or isovaleric acids, has been used to differentiate fusobacteria from other members of the family *Bacteroidaceae*. More recently, fusobacteria have been subdivided into species and subspecies by the comparative analysis of cellular fatty acid patterns and small-subunit rRNA gene sequences (1,3,4).

Fusobacteria, either alone or in combination with other anaerobes and aerobes, have been isolated from a wide variety of clinically significant anaerobic infections. However, positive identifications cannot always be made because these bacteria require specific growth conditions, appear with varying cell morphologies, and give primarily negative responses in routine biochemical tests (5). On the other hand, the occurrence of fusobacteria as part of the normal flora of the oral cavity, female genital tract, and gastrointestinal tract (5-7) provides many opportunities for these bacteria to initiate infections.

PERIODONTAL DISEASES

Severe destructive periodontal diseases affect 5-20% of the population, at considerable social and economic costs (8,9). These diseases are characterized by local tissue inflammation, tissue destruction, and bone loss (8). Periodontal diseases, which eventually result in the loss of teeth, can also have a variety of systemic effects (8,10). It is well known that transient bacteremias can occur as a result of normal oral hygiene practices, such as the brushing of teeth (10,11). Such transient bacteremias can cause complications in susceptible patients. For example, patients with damaged heart valves or prosthetic devices are susceptible to infective endocarditis or infection of the prosthesis (10,12,13), and precautions are taken to avoid complications due to transient bacteremias arising from professional dental care (12). Infection by *Chlamydia pneumoniae* and other microbial factors have been implicated as risk factors for atherogenesis (14-16), and many epidemiologic studies have indicated that patients suffering from periodontitis are also at an increased risk of developing coronary ar-

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tery disease (CAD) (17-19). A cross-sectional study by Mattila *et al.* (18) has suggested that dental infections, particularly gingivitis and periodontal diseases, are as important as the classical risk factors (age, smoking, diabetes, hypertension, and elevated serum triglycerides) in the pathogenesis of CAD. DeStefano *et al.* carried out a prospective cohort study (9760 subjects followed for a median of 14 years) in which it was determined that men under 50 with periodontitis had a stronger risk for CAD, but overall, they found that periodontal disease was associated with a small increased risk (19). Diabetic patients may have a reduced need for insulin following treatment for periodontitis (10,20,21), and it has been noted that potential respiratory pathogens may become established in the oral flora of patients with periodontal disease (10). A number of studies which examined the relationship between oral health and the sense of well-being, especially in the elderly, have concluded that eating difficulties lead to social withdrawal, especially in the elderly (10,22,23).

Infectious periodontal diseases, including gingivitis and periodontitis, are complex, multifactorial diseases, primarily due to the interaction between organisms and the immune system (1). Many reviews have described the pathogenesis in detail (1,2,24-29); a simplified summary follows. The initial event in periodontal diseases is the growth of predominantly aerobic, saccharolytic bacteria along a clean gingival margin (30,31). These early colonizers are primarily Gram-positive streptococci and Gram-positive rods which are capable of adhering to human tissues, such as tooth enamel and gingiva. The anaerobic, asaccharolytic bacteria (1,2) responsible for periodontal diseases do not adhere directly to human tissue, and buildup of these species occurs by coaggregation with other bacteria, a phenomenon particularly associated with oral bacteria (1,30). The interactions among the various genera and species colonizing the oral mucosa (1,30,32-38) are cell specific; the late colonizers found in periodontal diseases do not coaggregate with the early colonizers. The ability of *Fusobacterium nucleatum* to coaggregate with most early and late colonizers (1,30) suggests that it acts as a microbial bridge between the early and late stages of infection (1,30,36,38). Because of this role, relatively large quantities of *F. nucleatum* are often found in subgingival pockets affected by periodontal disease (1,39-41). While *F. nucleatum* coaggregates with the three microorganisms that are normally implicated in the etiology of periodontal diseases (1,30) - *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Bacteroides forsythus* - the relationship between *F. nucleatum* and *P. gingivalis* appears particularly strong (1,35,36).

F. nucleatum, being part of the normal oral flora, can be isolated from the healthy gingiva of most adults (6,42). This is not to say, however, that the organism is benign; the many virulence factors that enable it to be pathogenic in periodontal diseases are likely to be quite important in systemic diseases as well. The lipopolysaccharide (LPS) in the cell wall of *F. nucleatum* is structurally related to the LPS of other Gram-negative bacteria, and has a biological activity similar to that of *Escherichia coli* (1,43-45). In addition to its toxic properties, the LPS of *F. nucleatum* activates complement, provoking an inflammatory response, resulting in further tissue destruction (1,2,46). The production of butyric acid by fusobacteria inhibits the proliferation of gingival fibroblasts which normally compromises the rapid healing of wounds (1,47,48).

The outer membrane proteins (OMPs) of *F. nucleatum* have a role in bacterial nutrition (1) and may play a role in the pathogenesis of adult periodontitis (49). OMPs in *F. nucleatum* display bioactivities similar to those of LPS, but are present in greater quantities (49). In other Gram-negative bacteria, OMPs provide a route for the uptake of antibiotics, and the OMPs in *F. nucleatum* may display similar activities (1,50). Evidence for the production of extracellular proteolytic enzymes by fusobacteria is weak (51,52), although its occurrence cannot be discounted (53).

LEMIERRE'S SYNDROME

Lemierre's syndrome (synonyms: postanginal sepsis, necrobacillosis) classically presents with a severe sore throat, followed by fever, rigors, and painful cervical lymphadenopathy in a previously healthy child or young adult (6,54-58). Jaundice may also be present (57). Both exudative and non-exudative tonsillar and peritonsillar abscesses, and/or lesions in the mouth and jaw may be present (56). Lemierre reported that the syndrome, which he referred to as "postanginal septicemia", may result following otitis media, mastoiditis, appendicitis, urinary tract infection, or "purulent" endometritis following parturition (56). Of these alternative presentations, otitis media is most frequently encountered, but overall, Lemierre's syndrome has not been very common in the antibiotic era (6,57-59). Recently, there has been some disagreement as to whether Epstein-Barr virus (EBV) may predispose patients to this condition (6,55).

Infections of *Fusobacterium necrophorum* are responsible for Lemierre's syndrome. Following oropharyngeal infection, the jugular vein becomes palpable as bacteria begin to colonize it (as well as other local veins) (6,54,60). The suppurative internal jugular vein may be mistaken for lymphadenopathy (6,54). Septic emboli from the jugular vein allow distant metastatic spread of *F. necrophorum* to the lungs, as well as to the joints and central nervous system (CNS) (6, 57,58). As infection spreads to the lungs, multiple infiltrates quickly cavitate and can result in pleural effusion, empyema, and/or pneumothorax (54,57). Septic arthritis usually affects one or more large joints, such as the hip or knee (6). *F. necrophorum* meningitis can follow pharyngeal infection and may also be otogenic (59). Cranial palsies and brain abscesses leading to infarction are possible CNS sequelae (6,61).

Lemierre's syndrome is relatively easy to diagnose clinically and timely antibiotic therapy can prevent complications or death (54). However, rates of morbidity and mortality (mortality: 4-18%) remain high, partly because unfamiliarity with the disease leads to delays in diagnosis, underdiagnosis, and delays in the choice of a proper antimicrobial agent. Unfortunately, identification of the pathogen by culture is often the first indication of the disease (6), but

growth on solid media in a laboratory takes at least 48 hours. This emphasizes the need for a prompt clinical diagnosis (6,55,58,62). Computed tomography (CT) or ultrasound of the neck may be used to confirm involvement of the internal jugular vein (6). X-rays may be used to localize some cranial and pulmonary lesions, and to follow the progress of treatment. The fairly recent reviews by Eyken and Sinave *et al.* should be helpful in correctly diagnosing this syndrome (57,58). It is ironic that Lemierre himself stated: "The appearance and repetition several days after the onset of a sore-throat (and particularly of a tonsillar abscess) of severe pyrexial attacks with an initial rigor, or still more certainly the occurrence of pulmonary infarcts and arthritic manifestations, constitute a syndrome so characteristic that mistake is almost impossible"(56).

TROPICAL SKIN ULCERS

Tropical skin ulcers (synonyms: Naga sore, tropical septic ulcer, ulcus tropicum, tropical phagedenic ulcer, tropical sloughing phagedena) (63) are common among children and young adults in the tropics, but are not confined to these areas (64,65). Patients are predominantly between 5 and 15 years old, with those over 35 years of age being rarely affected (63). Although tropical skin ulcers are relatively common and are the leading cause of morbidity in parts of the tropics (65), they remain understudied. This is mainly because they usually occur in rural areas, away from large research centers (66). Much of what is known about the etiology and pathogenesis of tropical skin ulcers is due to epidemiologic studies by Adriaans, and an experimental study by McAdam, who induced these ulcers in 20 volunteers by bathing intact skin with ulcer pus for 6-10 days (63,67,68).

The major etiological factors of tropical skin ulcers have been identified as trauma and secondary infection. The trauma may be extremely minor, such as leg contact with previously infected shrubbery and plants (68). For this reason, the lesions usually occur on exposed skin (68,69). A small localized inflammatory reaction develops into a pustule about 1 cm in diameter after 5 or 6 days (68). Once the pustule ruptures, a foul-smelling blood-stained pus is discharged, and the round ulcer is raised above the surrounding edematous skin (68). The ulcer, which is usually solitary, involves the skin and subcutaneous tissues, but if the deep fascia is penetrated, the ulcer can destroy tendons, muscles, joints and bone (68,70). During its acute stage, the ulcer is extremely painful, leading to difficulties in sleeping and ambulating. An ulcer can bleed as much as 90 mL in 15 minutes (68). The margins of the ulcers often have what is described as pseudo-epitheliomatous hyperplasia (67); squamous carcinoma, perhaps due to the hyperplasia, occurs in about 2-15% of ulcers of more than 3 years duration (63). The nutritional status of the patient does not appear to be particularly relevant to the development of ulcers, as was once thought (63). Moisture is apparently necessary to induce infection and subsequent ulceration, as there is an increased incidence in the wet season (63,68). Patients often do not develop immunity to the infectious agents; it has been observed that recurrence of the ulcers is possible if patients are re-exposed to the causative organisms (63).

Fusobacteria are the most frequently isolated bacteria from early tropical ulcers, having been implicated in about 35% of all cases (67). *F. nucleatum*, *F. necrophorum*, and *F. ulcerans* are the species usually associated with this disease, and the rapid tissue destruction involved has led to the inference of bacterial toxin production (5,64,65).

INTRAAMNIOTIC INFECTION

Premature infants with low birth weights (<2500 g) are a major social and economic public health problem. A more intensive hospital-based management of low birth weight infants, and not a decline in incidence, has resulted in the most recent reductions of infant mortality in more developed nations (71-73). Although the exact pathogenesis of intraamniotic infection (IAI) (synonyms: clinical chorioamnionitis, amnionitis, amniotic fluid infection, intrapartum infection) is unknown, infection has been established as a major etiological factor in premature rupture of chorioamniotic membranes and as a cause of prematurity (74-79). The incidence of IAI has been reported to be 1-4% by Gibbs and Duff, although incidence rates up to 10.5% have also been described (74,75,80).

The hallmark of IAI is maternal fever, although uterine tenderness, foul-smelling amniotic fluid, maternal tachycardia, and fetal tachycardia have also been noted (74-76). Common maternal complications associated with IAI have been dysfunctional labor and postpartum infections (74,79,81). Neonatal complications are usually related to premature birth; the newborn may also be born with an infection or sepsis (78).

The bacteria most related to prematurity have been reported to be fusobacteria and group B streptococci (82). According to Altshuler and Hyde, fusobacterial infections have been associated with 18% of IAI cases that result in prematurity, but figures as high as 30% have been reported (77,83-88). Although the mechanism by which bacteria precipitate labor is unclear, translocation of endotoxins and maternally-produced prostaglandins in response to bacterial phospholipase A_2 have been implicated (71,77,89).

OTHER INFECTIONS

Case reports have documented the involvement of fusobacteria in osteomyelitis (90,91), urinary tract infections (92), pulmonary nodules (93), infective endocarditis (94), pericarditis (95), septic arthritis of the sternoclavicular joint (96), liver and splenic abscesses (97-100), fatal pneumonia (101), and disseminated intravascular coagulation (102), among others. In most of these infections, the most probable route of entry for fusobacteria is the oropharynx. Fusobacterial sternoclavicular infections are now exceedingly rare, but in the preantibiotic era, *F. necrophorum* was the most important anaerobe in these infections (96). However, splenic abscesses

may be more common in specific subgroups within the population, particularly intravenous drug users who have the habit of licking needles before injection to ease passage of the needle, to check the potency of the drug, and to ensure that the bevel is sharp (99,100).

Although *F. nucleatum* and *F. necrophorum* are considered the most pathogenic in this genus, other fusobacteria do occasionally cause infection. *F. russi* has been associated with animal bite infections, and *F. varium* with conjunctivitis and intra-ocular infections (5). *F. mortiferum* sepsis has been documented as well (103).

THE ROLE OF ANTIMICROBIAL THERAPY IN FUSOBACTERIAL INFECTIONS

In general, fusobacteria display variable resistance to vancomycin, erythromycin, amoxicillin, ampicillin, and aminoglycosides (*e.g.* neomycin) (1,101,104-109). There are no general guidelines for choosing an antimicrobial agent, but antibiotic susceptibility testing is advised if the case is not urgent. Otherwise, empiric use of broad spectrum antibiotics with activity against anaerobes will suffice (110). Some commonly used antibiotics for anaerobic coverage include metronidazole, imipenem, and penicillins (110).

In periodontal diseases, antibiotic therapy is usually directed against *P. gingivalis*, *B. forsythus*, and *A. actinomycetemcomitans*, and typically involves a combination of a common tetracycline or penicillin antibiotic with metronidazole or ciprofloxacin (29). Antibiotics can be administered systemically or locally in the periodontal pocket. *F. nucleatum* often displays resistance to tetracyclines, and beta-lactamase producing strains are becoming more common (1,106,108,111). It has been estimated that 40-60% of clinically isolated fusobacteria strains are beta-lactamase producing, but the clinical significance of this finding is not yet clear (110). Treatment of periodontal diseases is not usually directed toward elimination of *F. nucleatum*, although certainly many antibiotic therapies may act against this organism (29).

Despite *in vitro* susceptibility to a number of antibiotics, numerous case reports have documented the ineffectiveness of many antibiotics in treating *F. necrophorum* infections (Lemierre's syndrome). As a result, the drug of choice is a combination of metronidazole usually with a penicillin for aerobic coverage, although certainly other drugs may also be effective (1,6,24,53-55,59,60,62,90,101,102,112,113). Surgical interventions may be necessary in some cases (54). If treatment is delivered effectively, full recovery without sequelae is the rule unless there is cerebral involvement or osteomyelitis. Antibiotic treatment should be at least 6 weeks in duration for Lemierre's syndrome (58).

Antibiotics are effective in the early stages of tropical skin ulcers (64,68), but they should be administered systemically, as local application often causes sensitization (63,114). The epithelium usually begins healing around the margin of the ulcer within 24 hours of administration (68). For more severe ulcers, skin grafts may be necessary (68).

There is no broad agreement on the selection of antibiotics for IAI, but there is accordance that both antibiotic therapy and delivery are essential to cure this condition (75). Gibbs and Duff report that many retrospective and prospective studies have evaluated the use of a penicillin with an aminoglycoside (75).

CONCLUSION

Fusobacteria are capable of producing infections that result in significant morbidity and mortality. The presence of *F. nucleatum* in the mouth is critical to the development of periodontal diseases, which affect a significant proportion of elderly patients. *F. necrophorum* causes Lemierre's syndrome, an entity which is less common in the antibiotic era, but which can have potentially devastating consequences if unrecognized. Lemierre's syndrome usually affects young adults, and often begins as a pharyngeal infection. Tropical skin ulcers have been attributed to a number of different species of fusobacteria; although the incidence of these ulcers seems to be declining with better living standards, they remain a significant cause of morbidity in parts of the tropics. Fusobacteria, although not the most common cause of IAI, have been associated with a significant proportion of premature births. The incidence of prematurity does not appear to have declined. Fusobacterial infections can affect a wide range of age groups throughout the world. The presence of fusobacteria as part of the normal flora of the oropharynx, female genital tract, and gastrointestinal system appears to be critical to the pathogenesis of a number of these infections.

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Formoterol fumarate dihydrate

Oxeze® Turbuhaler®

(formoterol fumarate dihydrate)

6 µg/Metered Dose and 12 µg/ Metered Dose
Dry powdered inhalers for oral inhalation

THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTIONS AND CLINICAL PHARMACOLOGY

Pharmacodynamic Properties

Formoterol produces bronchodilation by stimulation of the β_2 adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of smooth muscle fibres.

Following inhalation of formoterol, a marked improvement in pulmonary function is observed within 1-3 minutes and lasts for a mean duration of 12 hours after a single dose.

Pharmacokinetic Properties

Absorption

Inhaled formoterol is rapidly absorbed. Peak plasma concentration is reached about 15 minutes after inhalation.

In studies the mean lung deposition of formoterol after inhalation via TURBUHALER ranged from 21-37% of the metered dose. The total systemic availability for the higher lung deposition was approximately 46% of the metered dose.

Distribution and Metabolism

Plasma protein binding is approximately 50%.

Formoterol is metabolized via direct glucuronidation and O-demethylation. The enzyme responsible for O-demethylation has not been identified. Total plasma clearance and volume of distribution has not been determined.

Elimination

The major part of the dose of formoterol is eliminated via metabolism. After inhalation 6-10% of the metered dose of formoterol is excreted unmetabolized in the urine. About 20% of an intravenous dose is excreted unchanged in the urine. The terminal half-life after inhalation is estimated to be 8 hours.

INDICATIONS AND CLINICAL USE

OXEZE TURBUHALER (formoterol fumarate dihydrate) is indicated for long-term, twice daily (morning and evening) administration in the maintenance treatment of asthma in patients 12 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, who are using optimal corticosteroid treatment and experiencing regular or frequent breakthrough symptoms requiring regular use of a short-acting bronchodilator. OXEZE TURBUHALER should not be used in patients whose asthma can be managed by occasional use of short-acting inhaled β_2-agonists.

Corticosteroids should not be stopped because formoterol is prescribed.

Formoterol is a long-acting β_2-agonist and should not be used as a rescue medication. To relieve acute asthmatic symptoms a short-acting inhaled bronchodilator (e.g., terbutaline or salbutamol) should be used.

CONTRAINDICATIONS

OXEZE TURBUHALER (formoterol fumarate dihydrate) is contraindicated when there is known hypersensitivity to formoterol or inhaled lactose. Like other sympathomimetic amines, OXEZE TURBUHALER should not be used in patients with tachyarrhythmias.

WARNINGS

Acutely Deteriorating Asthma

OXEZE TURBUHALER (formoterol fumarate dihydrate) should not be initiated or increased in patients with significantly worsening or acutely deteriorating asthma (see PRECAUTIONS).

Use of Anti-Inflammatory Agents

Patients should be receiving optimal anti-inflammatory therapy with corticosteroids before starting OXEZE TURBUHALER. Formoterol is not a substitute for inhaled or oral corticosteroids; its use is complementary to them. Corticosteroids should not be stopped when OXEZE TURBUHALER is initiated. Patients must be advised not to stop or reduce corticosteroid therapy without medical advice (see PRECAUTIONS).

Treatment of Acute Symptoms

OXEZE TURBUHALER should not be used to treat acute symptoms. It is crucial to advise patients accordingly and prescribe a short-acting, inhaled bronchodilator for this purpose. Medical attention should be sought if patients find that short-acting relief bronchodilator treatment becomes less effective or that they need more inhalations than usual (see PRECAUTIONS).

OXEZE TURBUHALER and the Management of Asthma

The management of asthma should normally follow a stepwise programme, with patient response monitored clinically and by lung function tests. Current asthma management guidelines recommend the following for long-acting β_2-agonists:

- Oral or inhaled corticosteroids should not be stopped.
- Adequate education should be provided to the patient regarding the use of long-acting β_2-agonists and the acute treatment of asthma, with close follow-up to ensure compliance.
- Long-acting β_2-agonists should not be introduced in significantly worsening or acutely deteriorating asthma.
- Long-acting β_2-agonists should never be used as rescue medication.

Increasing use of short-acting inhaled β_2-agonists to control symptoms indicates deterioration of asthma control and the need to reassess the patient's therapy.

Sudden or progressive deterioration in asthma control is potentially life-threatening; the treatment plan must be re-evaluated, and consideration be given to increasing corticosteroid therapy. In patients at risk, daily peak flow monitoring with precise instructions for acceptable variation limits should be considered.

Cardiovascular and Hypokalemic Effects

Potentially serious ECG changes (such as increased QTc interval) and hypokalemia may result from β_2-agonist therapy. Although clinically not significant, a small increase in QTc interval and/or decrease in serum potassium has been reported at therapeutic doses of formoterol. Particular caution is advised in severe asthma as these effects may be potentiated by hypoxia and concomitant treatment with xanthine derivatives, steroids and diuretics. Hypokalemia will increase the susceptibility of digitalis patients to cardiac arrhythmias (see PRECAUTIONS). It is recommended that serum potassium levels be monitored in such situations. Therefore, OXEZE TURBUHALER, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, arrhythmias and hypertension.

Other Diseases

Sympathomimetic bronchodilators should be administered cautiously to patients who are unusually responsive to sympathomimetic amines, e.g., in patients with hyperthyroidism not yet under adequate control. Since β_2-agonists may increase the blood glucose level, additional blood glucose controls are recommended when asthmatic patients with concomitant diabetes are started on OXEZE TURBUHALER.

Paradoxical Bronchospasm

As with other inhaled asthma medication, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, treatment with OXEZE TURBUHALER should be discontinued immediately and alternative therapy instituted.

Postmarketing Experience

The postmarketing experience with OXEZE TURBUHALER is limited. Postmarketing experience with other long-acting β_2-agonists (formoterol and salmeterol) have reported serious exacerbations of asthma including some that have been fatal. In most cases, these have occurred in patients with severe asthma and/or in some patients whose asthma has been acutely deteriorating (see WARNINGS), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether long-acting β_2-agonists contributed to these events or simply failed to relieve the deteriorating asthma.

PRECAUTIONS

Do Not Introduce OXEZE TURBUHALER As A Treatment For Acutely Deteriorating Asthma

OXEZE TURBUHALER (formoterol fumarate dihydrate) is intended for the maintenance treatment of asthma (see INDICATIONS AND CLINICAL USE) and should not be introduced or increased in acutely deteriorating asthma, which is a potentially life threatening condition. In patients with worsening asthma, there are no data demonstrating that long-acting β_2-agonists provide greater efficacy than or additional efficacy to short-acting, inhaled β_2-agonists. With other long-acting β_2-agonists, serious acute respiratory events, including fatalities, have been reported, some of which have occurred in patients with severe asthma and/or patients in whom asthma has been acutely deteriorating. Although it is not possible from these reports to determine the causal relationship between long-acting β_2-agonists and these adverse events, the introduction or increased use of a long-acting β_2-agonist in patients with acutely deteriorating asthma is inappropriate.

Do Not Use OXEZE TURBUHALER as a Substitute for Oral or Inhaled Corticosteroids

Patients who require therapy with OXEZE TURBUHALER should also receive optimal anti-inflammatory therapy with corticosteroids. Patients must be advised to continue taking their anti-inflammatory therapy after the introduction of OXEZE TURBUHALER even when symptoms decrease. Any change in corticosteroid dosage should be made ONLY after clinical evaluation.

Do Not Use OXEZE TURBUHALER to Treat Acute Symptoms

OXEZE TURBUHALER should only be used in patients requiring long-term regular bronchodilator therapy and NOT as an alternative to short-acting beta-agonists used "on demand" or in the event of an acute attack.

OXEZE TURBUHALER should NOT be used to relieve acute asthma symptoms. When prescribing OXEZE TURBUHALER, the physician must also provide the patient with a short-acting, inhaled β_2-agonist (e.g., terbutaline or salbutamol) for treatment of symptoms that occur acutely, despite regular twice-daily use of OXEZE TURBUHALER.

Although formoterol has a rapid onset of action (1 to 3 minutes), current asthma management guidelines recommend that long-acting inhaled bronchodilators should be used only as twice-daily maintenance bronchodilator therapy.

Watch for Increased Need for Short-Acting, Inhaled β_2-Agonists

Bronchodilators of the short-acting adrenergic stimulant type may be used for relief of breakthrough symptoms while using formoterol. Asthma may deteriorate acutely over a period of hours or slowly over several days or longer. Should symptoms persist, or treatment with short-acting inhaled β_2-agonist become less effective or a patient needs more inhalations than usual, this indicates a worsening of the underlying condition and warrants reassessment of the treatment regimen and consideration given to increasing corticosteroid therapy. Increasing the daily dosage of OXEZE TURBUHALER in this situation is not appropriate. Patients requiring increasing doses or inhalations of short-acting β_2-agonists for relief of symptoms should be advised to consult a physician for re-evaluation.

Do Not Exceed Recommended Dosage

OXEZE TURBUHALER should NOT be used more frequently than twice daily or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs (see below).

Cardiovascular and Other Medical Conditions

Usually no effect on the cardiovascular or central nervous system is seen after the administration of formoterol at recommended doses, but the cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased heart rate, cardiac contractility, tremor) can occur while using formoterol. Special care and supervision, with particular emphasis on dosage limits, is required in patients receiving OXEZE TURBUHALER when the following conditions may exist: ischemic heart disease, cardiac arrhythmias, especially third degree atrioventricular block, severe cardiac decompensation, severe hypertension, hypertrophic obstructive cardiomyopathy, thyrotoxicosis or severe heart failure.

Use with caution in patients with idiopathic hypertrophic subvalvular aortic stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

Caution should be observed when treating patients with known or suspected prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of OXEZE TURBUHALER. OXEZE TURBUHALER contains lactose (600 µg per metered dose) and is contraindicated in patients with hypersensitivity to inhaled lactose or formoterol. The amount of lactose in OXEZE TURBUHALER does not normally cause problems in lactose intolerant people (see CONTRAINDICATIONS).

Metabolic Effects

Due to the reversible hyperglycemic effect of β_2-agonists, additional blood glucose monitoring is recommended initially in diabetic patients.

Use in Women

Pregnant Women

The safety of OXEZE TURBUHALER during pregnancy has not yet been established (see Use in Labour and Delivery).

Lactating Women

Formoterol was found to be excreted in the milk of lactating rats after oral administration. Since there is no experience in the use of OXEZE TURBUHALER in nursing mothers, its use in such circumstances should only be considered if the expected benefit to the mother is greater than the risk to the infant.

Use in Labour and Delivery

There are no well-controlled human studies that have investigated the effects of formoterol on preterm labour or labour at term. Because of the potential for β-agonist interference with uterine contractibility, use of β_2-agonists, such as OXEZE TURBUHALER, during labour should be restricted to those patients in whom the benefits clearly outweigh the risks.

Use in Geriatrics

No adjustment of dose should be required in the elderly, or in patients with renal or hepatic impairment, at the recommended normal doses. (See also WARNINGS and PRECAUTIONS for patients with cardiovascular disorders).

Use in Pediatrics

OXEZE TURBUHALER is not currently recommended for use in children younger than 12 years of age due to limited clinical data in this age group.

Use in Adolescent Patients and Asthma Severity Reassessment

In adolescent patients the severity of asthma may be variable with age and periodic reassessment should be considered to determine if continued maintenance therapy with OXEZE TURBUHALER is still indicated. Compliance, especially neglect of anti-inflammatory therapy and overuse of short-acting β_2-agonists, should be carefully followed in adolescents receiving long-acting β_2-agonists.

Drug Interactions

Beta-Receptor Blocking Agents

Beta-receptor blocking agents, especially non-selective ones, may partly or totally inhibit the effect of beta-stimulants.

Should a patient treated with OXEZE TURBUHALER also require concomitant treatment with a beta-blocker, it is recommended that a beta-blocker (e.g., metoprolol) with less predominant β_2-blocking effects be considered. If concomitant treatment is necessary, patients should be monitored carefully for possible deterioration in pulmonary function and the need to adjust the dosage of either drug.

Xanthine Derivatives, Steroids and Diuretics

Concomitant treatment with xanthine derivatives, steroids or diuretics may potentiate a possible hypokalemic effect of β_2-agonists. Hypokalemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides.

Other Drugs

Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias.

L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards β_2-sympathomimetics.

Concomitant treatment with monoamine oxidase inhibitors including agents with similar properties such as furazolidone and procarbazine may precipitate hypertensive reactions.

There is elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.

Information to be Provided to the Patient

See illustrated INFORMATION FOR THE CONSUMER section. It is important that patients understand how to use OXEZE TURBUHALER and how it should be used in relation to other asthma medications they are taking. Patients should be given the following information:

i. The recommended dosage, as follows:

Adults: The usual dose is 6 or 12 µg, twice daily, at 12 hour intervals. Some adults may need 24 µg, twice daily. The maximum daily dosage for adults, 48 µg, should not be exceeded.

Adolescent Children (12-16 years): The usual dose is 6 µg, twice daily, at 12 hour intervals. Some children may need 12 µg, twice daily. The maximum daily dosage for adolescent children, 24 µg, should not be exceeded.

OXEZE TURBUHALER is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with a short-acting, inhaled β_2-agonist such as terbutaline or salbutamol (the physician should provide the patient with such medication and instruct the patient in how it should be used).

ii. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma:

- Decreased effectiveness of short-acting, inhaled β_2-agonist
- Need for more inhalations than usual of short-acting, inhaled β_2-agonist.

iii. OXEZE TURBUHALER should not be used as a substitute for oral or inhaled corticosteroids. Patients must be advised to continue taking their corticosteriod therapy after the introduction of OXEZE TURBUHALER even when symptoms decrease.

iv. Patients should be cautioned regarding potential adverse cardiovascular effects, such as palpitations or chest pain.

v. In patients receiving OXEZE TURBUHALER other inhaled medications should be used only as directed by the physician.

vi. Parents/guardians of adolescent children who have been prescribed OXEZE TURBUHALER should be alerted to the general concern regarding asthma therapy compliance, especially neglect of anti-inflammatory therapy and overuse of short-acting β_2-agonists.

ADVERSE REACTIONS

Pharmacologically predictable side-effects of β_2-agonist therapy, such as tremor and palpitations, may occur but tend to be transient and reduced with regular therapy. As with other inhalation therapy, paradoxical bronchospasm may occur in very rare cases. The following adverse reactions can be classified as common (i.e. frequency ≥1% and <10%): tremor, palpitations and headache; uncommon (frequency ≥0.1% and <1%): muscle cramps, tachycardia, agitation, restlessness and sleep disturbances; very rare (frequency <0.01%): bronchospasm, exanthema, urticaria, pruritus and hypokalemia.

The clinical program conducted with OXEZE TURBUHALER, has involved more than 1,800 patients. The incidence of adverse events, irrespective of causality towards the drug, from four controlled trials (duration 1, 3, 3 and 6 months respectively) with OXEZE TURBUHALER is presented in the following table.

Table 1.

Incidence of adverse events (irrespective of causality) with frequency higher than placebo in four controlled trials of duration 1, 3, 3 and 6 months respectively.

	OXEZE TURBUHALER			Placebo TURBUHALER
	Total No. (%)	6 µg b.i.d. No. (%)	12 µg b.i.d. No. (%)	No. (%)
Total Number of Evaluable Patients	359	190	169	412
Headache	66 (18%)	15 (8%)	51 (30%)	84 (20%)
Tremor	11 (3%)	4 (2%)	7 (4%)	2 (0%)
Pharynx Disorder	18 (5%)	3 (2%)	15 (9%)	10 (2%)
Cramps	10 (3%)	3 (2%)	7 (4%)	3 (1%)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no clinical experience on the management of overdose. An overdose would likely lead to effects that are typical of β_2-adrenergic agonists: tremor, headache, palpitations and tachycardia. Hypotension, metabolic acidosis, hypokalemia and hyperglycemia may also occur. Supportive and symptomatic treatment may be indicated.

DOSAGE AND ADMINISTRATION

OXEZE TURBUHALER (formoterol fumarate dihydrate) should NOT be initiated or increased in patients with significantly worsening or acutely deteriorating asthma, which may be a life-threatening condition (see PRECAUTIONS).

OXEZE TURBUHALER should only be used in patients requiring long-term regular bronchodilator therapy in addition to optimal corticosteroid therapy and NOT as an alternative to short-acting beta-agonists used "on demand" or in the event of an acute attack.

OXEZE TURBUHALER SHOULD NOT BE USED TO TREAT ACUTE SYMPTOMS. It is crucial to inform patients of this and prescribe a short-acting, inhaled β_2-agonist for this purpose.

OXEZE TURBUHALER SHOULD NOT BE USED MORE FREQUENTLY THAN TWICE DAILY WITH A TWELVE-HOUR INTERVAL BETWEEN DOSES OR AT HIGHER DOSES THAN RECOMMENDED. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's short-acting inhaled β_2-agonist becomes less effective or a patient needs more inhalations than usual, this may be a marker of destabilization of asthma. In this setting, the patient requires immediate reassessment of the treatment regimen. Increasing the daily dosage of OXEZE TURBUHALER in this situation is not appropriate (see PRECAUTIONS).

Bronchodilators should not be the only or the main treatment in patients with moderate to severe or unstable asthma. Patients with severe asthma may require regular medical assessment. These patients will require high dose inhaled or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroids dosage which should be administered under medical supervision.

Since there may be serious adverse effects associated with excessive dosing, the dosage or frequency of administration should not be increased.

As a twice daily regular treatment, OXEZE TURBUHALER provides 24-hour bronchodilation and can replace regular use of a fast-acting, short duration inhaled bronchodilator (e.g., salbutamol or terbutaline), when used concurrently with corticosteroid therapy.

Dosage should be individualized and patient response should be monitored by the prescribing physician on an ongoing basis.

Long-Term Twice Daily Maintenance Therapy

The dose of OXEZE TURBUHALER should be individualized to the patient's needs and should be the lowest possible dose that keeps the patient symptom free or fulfills the therapeutic objective.

Adults:

The usual dose is 6 or 12 µg, twice daily, at 12 hour intervals. Some adults may need 24 µg, twice daily. The maximum daily dosage for adults, 48 µg, should not be exceeded.

Adolescent Children (12-16 years):

The usual dose is 6 µg, twice daily, at 12 hour intervals. Some children may need 12 µg, twice daily. The maximum daily dosage for adolescent children, 24 µg, should not be exceeded.

In adolescent patients, the severity of asthma may be variable with age and periodic reassessment should be considered to identify the lowest dose required to maintain control and to determine if continued maintenance therapy with OXEZE TURBUHALER is still indicated (see PRECAUTIONS).

OXEZE TURBUHALER is available in two strengths, 6 or 12 µg per inhalation. Use of the higher strength is recommended for patients requiring 12 µg or more, twice daily. OXEZE TURBUHALER is not currently recommended for children younger than 12 years of age due to the limited clinical data in this age group.

It is important to instruct patients to avoid exhaling into the device and to always replace the cover after using OXEZE TURBUHALER.

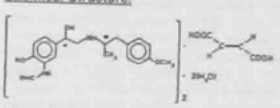
NOTE: The medication from OXEZE TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. The patient may not taste or feel any medication when using OXEZE TURBUHALER due to the small amount of drug dispensed.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: formoterol fumarate dihydrate

Chemical Structure:



Molecular Formula: $C_{42}H_{56}N_4O_{14}$

Molecular Weight: 840.9

Chemical Name: (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate

Description: Formoterol fumarate dihydrate is a white to off-white or slightly yellow non-hygroscopic crystalline powder.

Dissociation Constant: The pK_a of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.

Partition Coefficient: The octanol-water partition coefficient at 25°C is 2.6.

Composition

Active: Formoterol fumarate dihydrate 6 or 12 µg/inhalation.
Non-Medicinal: Lactose monohydrate.

Stability and Storage Recommendations

OXEZE TURBUHALER should be stored at room temperature between 15°C and 30°C with the cover tightened, away from moisture.

AVAILABILITY OF DOSAGE FORMS

OXEZE TURBUHALER (formoterol fumarate dihydrate) is supplied in two strengths: 6 µg/metered dose (60 doses) and 12 µg/metered dose (60 doses).

The strength of OXEZE TURBUHALER can be identified by the colour of the turning grip: the 6 µg/metered dose strength has a light greenish-blue turning grip, and the 12 µg/metered dose strength has a dark greenish-blue turning grip.

OXEZE TURBUHALER also contains lactose (600 µg per metered dose). This amount does not normally cause problems in lactose-intolerant people.

OXEZE TURBUHALER cannot be refilled and should be discarded when empty.

References:

1. Canadian Respiratory Journal 1996;3(2):89-100.
2. Pauwels R, et al. New England Journal of Medicine 1997;337:1405-1411.
3. Oxeze® Turbuhaler® Product Monograph.

Product Monograph available upon request

Budesonide

Pulmicort®

Turbuhaler®

Turn to control

100 µg, 200 µg and 400 µg dry powder inhalers for Oral Inhalation

THERAPEUTIC CLASSIFICATION

Glucocorticosteroid for the treatment of bronchial asthma.

INDICATIONS AND CLINICAL USE:

Patients with bronchial asthma: 1. In patients who require inhaled steroids, 2. In patients for whom a reduction of systemic glucocorticoids is desirable.

CONTRAINDICATIONS: 1. Status asthmaticus; not to be used in primary treatment of acute episodes of asthma or in patients with moderate to severe bronchiectasis, 2. Hypersensitivity to budesonide, 3. Active or quiescent pulmonary tuberculosis, 4. Untreated fungal, bacterial or viral infections of the respiratory system.

WARNINGS: 1. PULMICORT is not intended for rapid relief of acute episodes of asthma where an inhaled short-acting bronchodilator is required. If patients find short-acting bronchodilator treatment ineffective, or they need more inhalations than usual, medical attention must be sought. In this situation consideration should be given to the need for anti-inflammatory therapy, e.g., higher doses of inhaled budesonide or a course of oral corticosteroid. 2. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to inhaled corticosteroids; therefore particular care is needed in patients who are transferred from systemically active corticosteroids to PULMICORT (budesonide). After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis, or other conditions associated with severe electrolyte loss. Although PULMICORT may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid which is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large dosages) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level. Patients previously on high doses of systemic steroids may regain earlier symptoms not related to asthma such as rhinitis and eczema when transferred from oral therapy to PULMICORT. These symptoms are a result of the generally lower systemic steroid action which will be experienced. Patients may also suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. Temporary resumption of systemic steroids may be necessary to treat these conditions. 3. The development of pharyngeal and laryngeal candidiasis is cause for concern because the extent of its penetration of the respiratory tract is unknown. If oral pharyngeal candidiasis develops, appropriate anti-fungal therapy should be implemented to eradicate the infection. The incidence of candidiasis can generally be held to a minimum by having patients rinse their mouths out with water after each inhalation. (See DOSAGE AND ADMINISTRATION.) 4. Glucocorticosteroids may mask some signs of infection and new infections may appear during their use. 5. There is no evidence that control of asthma can be achieved by administration of PULMICORT in doses higher than those recommended. During such episodes, patients may require therapy with systemic corticosteroids.

PRECAUTIONS: 1. In transferring patients from a systemic steroid to PULMICORT (budesonide), the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g. joint and/or muscular pain, lassitude, depression) may occur in spite of maintenance or improvement of respiratory functions. (See DOSAGE AND ADMINISTRATION). 2. It is essential that the patient be instructed that PULMICORT is a preventative agent which must be taken at regular intervals and is not to be used to relieve an acute asthmatic attack. 3. The long-term effects of budesonide on developmental or immunologic processes in the mouth, pharynx, trachea, eyes, and lung are unknown. With the recommended therapeutic doses of PULMICORT, there is little risk of adverse systemic effects. 4. In children, treated for 2 to 6 years, with budesonide via TURBUHALER® at daily doses up to 400 µg, no effect was demonstrated on statural growth compared with nonsteroidal therapy. However, to allow for individuals that are excessively sensitive, it is recommended that height is monitored in growing children. 5. Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually. 6. Pulmonary infiltrates with eosinophilia may occur in patients on PULMICORT therapy. Although this is possible in some patients who are administered inhalational steroids, their causative role cannot be ruled out. 7. **Usage During Pregnancy.** Administration of PULMICORT during pregnancy should be avoided unless there are compelling reasons. In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats, and mice. The relevance of these findings to humans has not yet been established. In the absence of further studies in humans, budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids, especially oral steroids, during pregnancy should be carefully observed for hypoadrenalism. 8. **Lactation.** Glucocorticoids are secreted in human milk. It is not known whether budesonide would be secreted in human milk, but it is suspected to be likely. The use of PULMICORT in nursing mothers requires that the possible benefits of the drug be weighed against the potential hazards to the mother, or infant. 9. **Children Under 6 Years of Age.** PULMICORT is not presently recommended for children younger than 6 years of age due to limited clinical data in this age group. 10. Corticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during corticosteroid therapy. During long-term therapy, pituitary-adrenal function and height (in children) should be periodically assessed. 11. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids. 12. There may be enhanced systemic effects of budesonide in patients with an advanced liver cirrhosis, and in those with hyperthyroidism. Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide however, are similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide were affected by compromised liver function as evidenced by increased systemic availability. This is however, of little importance for PULMICORT, as after inhalation the oral contribution to the systemic availability is very small. 13. Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. 14. Special care is needed in patients with lung tuberculosis and fungal and viral infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops treatment with antiviral agents may be considered. If, however, a viral upper respiratory infection is present, the patient should adhere to the regular asthma medication. In patients who are known to deteriorate rapidly when they have a viral respiratory infection, a short course of oral corticosteroid therapy should be considered. Clinical studies have shown that viral infections cause significantly fewer problems in patients who are on regular treatment with topical glucocorticosteroids. 15. To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of PULMICORT TURBUHALER®. 16. Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as Candida albicans. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: Budesonide has not been observed to interact with any drug used for the treatment of asthma. Cimetidine: The kinetics of budesonide were investigated in a study of healthy subjects without and with cimetidine 1000 mg daily. After a 4 mg oral dose the values for C_{max} (nmol/L) and systemic availability (%) of budesonide without and with cimetidine (3.3 vs 5.1 nmol/L and 10 vs 12%, respectively) indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of little clinical importance. Ketoconazole: Ketoconazole, a potent inhibitor of cytochrome P450 3A, the main metabolic enzyme for corticosteroids, increases plasma levels of orally ingested budesonide. Omeprazole: At recommended doses, omeprazole has no effect on the pharmacokinetics of oral budesonide.

ADVERSE REACTIONS: No major side effects attributable to the use of PULMICORT (budesonide), in all dosage forms, have been reported. During clinical trials, the frequency of subjectively reported side effects was low. The most common side effects were cough, throat irritation, and hoarseness (2-4%). Bad taste, headache, nausea and dryness of the throat were reported less frequently. Other side effects reported on occasion during budesonide treatment were tiredness, thirst, and diarrhea. Skin reactions (urticaria, rash, dermatitis, angioedema, etc.) may, in rare cases, occur in association with local corticosteroid therapy. In rare cases, skin bruising has been reported following treatment with inhaled glucocorticosteroids. Psychiatric symptoms such as nervousness, restlessness and depression, as well as behavioural disturbances in children, have been observed. As with other inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

In rare cases, signs or symptoms of systemic glucocorticosteroid effect including hypofunction of the adrenal gland and oropharyngeal complications may occur, depending on dose, exposure time, concomitant and previous steroid exposure, and individual sensitivity. Candidiasis has been reported by some patients and may occur at therapeutic doses. In patients in whom systemic steroids are reduced or stopped, withdrawal symptoms due to decreased systemic activity occur frequently. (See DOSAGE AND ADMINISTRATION: CLINICAL MANAGEMENT).

DOSAGE AND ADMINISTRATION

Adults and Children over 12 Years of Age. When treatment with inhaled glucocorticosteroids is started, during periods of severe asthma, and while reducing or discontinuing oral glucocorticosteroids the dosage should be 400-2400 µg daily divided into 2-4 administrations. The maintenance dose is usually 200-400 µg twice daily but higher doses may be necessary for longer or shorter periods of time in some patients. The dose of PULMICORT (budesonide) should be individualized to the patient's need and should be the lowest possible dose that fills the therapeutic objective. Once daily dosing may be considered in patients who require a dosage of 400 µg budesonide per day. The dose may then be given in the morning or in the evening. If deterioration of asthma occurs, the frequency of dosing and the daily dose should be increased.

Treatment with PULMICORT should not be stopped abruptly, but tapered off gradually.

Children 6-12 Years. When starting therapy with budesonide in children, during periods of severe asthma and while reducing or discontinuing oral corticosteroids, the dosage should be 200-400 µg daily, given in divided doses twice daily at 100 to 200 micrograms per inhalation. The maintenance dose is individual and should be the lowest dose which keeps the patient symptom-free. Administration twice daily is usually adequate in stable asthmatics.

Children Under 6 Years of Age. Not recommended in children in this age group.

Clinical studies in man have shown an improved efficacy for the same amount of budesonide delivered via TURBUHALER® inhaler as compared with the pressurized aerosol with NEBUHALER® spacer device. It may be possible to reduce the dose of PULMICORT TURBUHALER when the patient is in a stable phase.

Approximately 30% of the metered dose is deposited in the lungs.

In patients where an increased therapeutic effect is desired, an increased dose of PULMICORT TURBUHALER is recommended because of the lower risk of systemic effects as compared with a combined treatment with oral glucocorticosteroids.

TURBUHALER®: TURBUHALER is a breath-activated dry powder inhaler which does not require a coordinated inhalation technique. It contains only the active ingredient budesonide – no propellants or preservatives, and as such, offers those patients sensitive to excipients an alternative dosage form. **NOTE: The patient may not taste or feel any medication when inhaling from TURBUHALER. This lack of feeling does not mean that the patient is not receiving benefit from PULMICORT TURBUHALER. NOTE: The medication from PULMICORT TURBUHALER is delivered to the lungs as the patient inhales and, therefore, it is important to instruct the patient to breathe in forcefully and deeply through the mouthpiece. When prescribing PULMICORT TURBUHALER to young children it is necessary to ascertain that they can follow the instructions for use. The patient may not taste or feel any medication when using PULMICORT TURBUHALER due to the small amount of drug dispensed. Patients should be instructed to rinse their mouths out with water after each inhalation. This will help prevent the occurrence of candidiasis. Cleansing dentures has the same effect.**

CLINICAL MANAGEMENT

Patients – Non-Steroid Dependent

Treatment with the recommended doses of PULMICORT usually gives a therapeutic effect within 10 days. However, certain patients might have an excessive collection of mucous secretion in the bronchi which reduces the penetration of the active substance in PULMICORT into the bronchial mucosa. In these cases, it is desirable to initially give a short (about 2 weeks) oral corticosteroid regimen in addition to PULMICORT. The oral treatment is started on a rather large dose which is then gradually reduced. Thereafter, treatment with PULMICORT only is sufficient. Exacerbations of the asthma caused by bacterial infections are controlled by adequate antibiotic regimens and also by increasing the PULMICORT dosage.

Patients – Steroid Dependent

Transferal of patients dependent upon oral steroids to treatment with PULMICORT demands special care mainly because of the slow restitution of the disturbed hypothalamic-pituitary-adrenal function caused by extended treatment with oral corticosteroids. When PULMICORT treatment is initiated, the patient should be in a relatively stable phase. PULMICORT is then given in combination with the previously used oral steroid dose for about 10 days. After this period of time, reduction of the oral corticoid dose may be started gradually. The oral dose is thus reduced to the lowest level which, in combination with PULMICORT, gives a stable respiratory capacity.

In adults, the usual rate of withdrawal of the systemic corticosteroid is the equivalent of 2.5 mg of prednisone every four days if the patient is under close observation. **If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower,** approximately 2.5 mg of prednisone (or equivalent) every 10 days. A slow rate of withdrawal cannot be overemphasized. If withdrawal symptoms appear, the previous dosage of the systemic drug should be resumed for a week before further decrease is attempted. During withdrawal, some patients may experience symptoms of systemically active steroid withdrawal, eg., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Such patients should be encouraged to continue with PULMICORT, but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dosage should be boosted temporarily and thereafter further withdrawal should continue more slowly.

In many cases it may be possible to completely replace the oral steroid with PULMICORT treatment. In other patients, a low oral steroid maintenance dosage may be required. The length of time needed for the body to regain its natural production of corticosteroid in sufficient quantity is often extended. **Thus, during severe asthma attacks or physically stressing situations such as severe infections, trauma, and surgical operations, it is necessary to resume systemic steroids (in large dosages) in order to avoid adrenocorticoid insufficiency.** Acute exacerbations, especially in connection with increased viscosity and mucous plugging, may require complementary treatment with a short course of oral corticosteroids which are gradually tapered as symptoms subside.

During transfer from oral therapy to PULMICORT, a lower general steroid action is experienced. The patients might regain earlier symptoms (rhinitis, eczema) or suffer from tiredness, headache, pain in muscles and joints and, occasionally, nausea and vomiting. In these cases, further medical support may be required.

AVAILABILITY OF DOSAGE FORMS: PULMICORT TURBUHALER is a dry powder inhaler containing 200 doses of 100 µg, 200 µg, and 400 µg or 100 doses of 200 µg of micronized budesonide. Each inhalation from PULMICORT TURBUHALER will provide either 100 µg, 200 µg or 400 µg of budesonide active substance; no additives or carrier substances are included. PULMICORT TURBUHALER cannot be re-filled and should be discarded when empty.

Product monograph available on request. 01/98

References:

1. Canadian Thoracic Society. Canadian Asthma Consensus Conference Summary of Recommendations. Canadian Respiratory Journal 1996;3(2):89-100. 2. Duncan J, et al. Clinical Assessment of a New Multidose Nonpressurised Metered-Dose Inhaler. Drug Invest. 1990; 2(2): 136-137. 3. Thorsson L, et al. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler pMDI. Eur Respir J 1994; 7:1839-1844.

ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

COZAAR®

losartan potassium

Tablets 25, 50 and 100 mg

Angiotensin II Receptor Antagonist

ACTION AND CLINICAL PHARMACOLOGY

COZAAR® (losartan potassium) antagonizes angiotensin II by blocking the angiotensin type one (AT_1) receptor.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system. Its effects include vasoconstriction and the stimulation of aldosterone secretion by the adrenal cortex.

Losartan, and its active metabolite, E-3174, block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to AT_1 receptors found in many tissues, including vascular smooth muscle. A second type of angiotensin II receptor has been identified as the AT_2 receptor, but it plays no known role in cardiovascular homeostasis to date. Both losartan and its active metabolite do not exhibit any agonist activity at the AT_1 receptor, and have much greater affinity, in the order of 1000-fold, for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan itself is a reversible, competitive antagonist at the AT_1 receptor, while the active metabolite is 10 to 40 times more potent than losartan, and is a reversible, non-competitive antagonist of the AT_1 receptor.

Neither losartan nor its active metabolite inhibits angiotensin converting enzyme (ACE), also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Pharmacokinetics

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P-450 enzymes. It is converted, in part, to an active carboxylic acid metabolite, E-3174, that is responsible for most of the angiotensin II receptor antagonism that follows oral losartan administration.

The terminal half-life of losartan itself is about 2 hours, and that of the active metabolite, about 6-9 hours. The pharmacokinetics of losartan and this metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily administration.

Following oral administration, losartan is well absorbed, with systemic bioavailability of losartan approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite, although about 1% of subjects did not convert losartan efficiently to the active metabolite.

Mean peak concentrations of losartan occur at about one hour, and that of its active metabolite at about 3-4 hours. Although maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times greater than that of losartan.

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Various losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, E-3174, several inactive metabolites are formed. *In vitro* studies indicate that cytochrome P-450 isoenzymes 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites.

The volume of distribution of losartan is about 34 liters, and that of the active metabolite is about 12 liters.

Total plasma clearance of losartan is about 600 mL/min, with about 75 mL/min accounted for by renal clearance. Total plasma clearance of the active metabolite is about 50 mL/min, with about 25 mL/min accounted for by renal clearance. Both biliary and urinary excretion contribute substantially to the elimination of losartan and its metabolites.

Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Pharmacodynamics

Losartan inhibits the pressor effect of angiotensin II. A dose of 100 mg inhibits this effect by about 85% at peak, with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity, and a consequent rise in angiotensin II plasma concentration, in hypertensive patients.

Maximum blood pressure lowering, following oral administration of a single dose of losartan, as seen in hypertensive patients, occurs at about 6 hours.

In losartan-treated patients during controlled trials, there was no meaningful change in heart rate.

There is no apparent rebound effect after abrupt withdrawal of losartan therapy.

Black hypertensive patients show a smaller average blood pressure response to losartan monotherapy than other hypertensive patients.

INDICATIONS AND CLINICAL USE

COZAAR® (losartan potassium) is indicated for the treatment of essential hypertension.

COZAAR® may be used alone or concomitantly with thiazide diuretics.

A great majority of patients with severe hypertension in controlled clinical trials required combination therapy. COZAAR® has been used concomitantly with beta-blockers and calcium channel blockers, but the data on such use are limited.

COZAAR® should normally be used in those patients in whom treatment with diuretic or beta-blocker was found ineffective or has been associated with unacceptable adverse effects. COZAAR® can also be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors have not been established.

CONTRAINDICATIONS

COZAAR® (losartan potassium) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, COZAAR® (losartan potassium) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of losartan potassium as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, losartan potassium should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as means of reversing hypotension and/or substituting for impaired renal function. Neither losartan nor the active metabolite can be removed by hemodialysis.

Animal data: Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, which include decreased body weight, mortality and/or renal toxicity. Significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of losartan, in some cases after the first dose. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

PRECAUTIONS

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of losartan should include appropriate assessment of renal function.

Patients with Impaired Liver Function

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan and its active metabolite in cirrhotic patients after administration of COZAAR® (losartan potassium), a lower dose should be considered for patients with hepatic impairment, or a history of hepatic impairment (see DOSAGE AND ADMINISTRATION, and PHARMACOLOGY).

Valvular Stenosis

There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Use in Nursing Mothers

It is not known whether losartan or its active metabolite are excreted in human milk, however significant levels of both of these compounds have been shown to be present in the milk of lactating rats. Because many drugs are excreted in human milk, and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children

Safety and effectiveness have not been established.

Use in the Elderly

Of the 2085 patients that received losartan monotherapy in controlled clinical trials, 391 (19%) were 65 years and over. No overall differences in safety were observed between these patients and younger patients, but appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population.

DRUG INTERACTIONS

Diuretics

Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with COZAAR®. The possibility of symptomatic hypotension with the use of COZAAR® can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of losartan (see WARNINGS – Hypotension, and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents Increasing Serum Potassium

Since COZAAR® decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.

Lithium Salts

As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

Digitalis

In 9 healthy volunteers, when a single oral dose of 0.5 mg digoxin was administered to patients receiving losartan for 11 days, digoxin AUC and digoxin C_{max} ratios, relative to placebo, were found to be 1.06 (90% C.I. 0.98 - 1.14) and 1.12 (90% C.I. 0.97 - 1.28), respectively. The effect of losartan on steady-state pharmacokinetics of cardiac glycosides is not known.

Warfarin

Losartan administered for 7 days did not affect the pharmacokinetics or pharmacodynamic activity of a single dose of warfarin. The effect of losartan on steady-state pharmacokinetics of warfarin is not known.

Drugs Affecting Cytochrome P-450 System

When losartan was administered to 10 healthy male volunteers as a single dose in steady-state conditions of phenobarbital, a cytochrome P-450 inducer, losartan AUC, relative to baseline, was 0.80 (90% C.I. 0.72 - 0.88), while AUC of the active metabolite, E-3174, was 0.80 (90% C.I. 0.78 - 0.82).

When losartan was administered to 8 healthy male volunteers as a single dose in steady-state conditions of cimetidine, a cytochrome P-450 inhibitor, losartan AUC, relative to baseline, was 1.18 (90% C.I. 1.10 - 1.27), while AUC of the active metabolite, E-3174, was 1.00 (90% C.I. 0.92 - 1.08).

ADVERSE REACTIONS

COZAAR® (losartan potassium) has been evaluated for safety in more than 3300 patients treated for essential hypertension. Of these, 2085 were treated with losartan monotherapy in controlled clinical trials.

In open studies, over 1200 patients were treated with losartan for more than 6 months, and over 800 for more than one year.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences occurred in 2.3% and 3.7% of patients treated with COZAAR® and placebo, respectively.

The following potentially serious adverse reactions have been reported rarely with losartan in controlled clinical trials: syncope, hypotension.

In these double-blind controlled clinical trials, the following adverse reactions reported with COZAAR® occurred in ≥1% of patients, regardless of drug relationship:

	COZAAR® (n=2085)	Placebo (n=535)
Body as a Whole		
Asthenia/fatigue	3.8	3.9
Edema/swelling	1.7	1.9
Abdominal pain	1.7	1.7
Chest pain	1.1	2.6
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Digestive		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

In these controlled clinical trials, dizziness was the only adverse experience, occurring in more than 1% of cases, that was reported as drug-related, and that occurred at a greater incidence in losartan-treated (2.4%) than placebo-treated (1.3%) patients.

In double-blind, controlled clinical trials, the following adverse reactions were reported with COZAAR® at an occurrence rate of less than 1%, regardless of drug relationship: orthostatic effects, somnolence, vertigo, epistaxis, tinnitus, constipation, malaise, rash.

Other adverse reactions reported rarely in open-label studies or post-marketing use, regardless of drug relationship, include asthenia, diarrhea, migraine, myalgia, pruritus, taste disorder and urticaria.

Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in patients treated with losartan.

LABORATORY TEST FINDINGS

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of COZAAR®.

Liver Function Tests: In patients treated with losartan monotherapy in double-blind hypertensive trials, elevations of AST 1.1% and ALT 1.9% occurred, compared with placebo values of 0.8% and 1.3% respectively. When AST or ALT elevations ≥ 2X upper limit of normal were compared, the frequency was similar to that seen in placebo.

Hyperkalemia: In controlled hypertensive trials, a serum potassium > 5.5 mEq/L occurred in 1.5% of patients, however, no patient discontinued losartan therapy due to hyperkalemia.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with COZAAR® alone. No patient discontinued taking COZAAR® alone due to increased BUN or serum creatinine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 gram percent and 0.09 volume percent, respectively) occurred frequently in patients treated with COZAAR® alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

In clinical trials, the following were noted to occur with an incidence of < 1%, regardless of drug relationship: thrombocytopenia, eosinophilia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available in regard to overdosage with COZAAR® (losartan potassium) in humans. The most likely manifestation of overdosage would

be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor the active metabolite can be removed by hemodialysis.

DOSAGE AND ADMINISTRATION

The dosage of COZAAR® (losartan potassium) must be individualized.

Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with COZAAR® may need to be adjusted.

Dosing should occur at about the same time each day. COZAAR® may be administered with or without food, however it should be taken consistently with respect to food intake.

Monotherapy

The usual starting dose of COZAAR® is 50 mg once daily.

Dosage should be adjusted according to blood pressure response. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy.

The usual dose range for COZAAR® is 50 to 100 mg once daily. A dose of 100 mg daily should not be exceeded, as no additional antihypertensive effect is obtained with higher doses.

In most patients taking COZAAR® 50 mg once daily, the antihypertensive effect is maintained. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. This can be evaluated by measuring the blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dosage, or an increase in the dose should be considered. If blood pressure is not adequately controlled with COZAAR® alone, a non-potassium-sparing diuretic may be administered concomitantly.

For patients with volume-depletion, a starting dose of 25 mg once daily should be considered (see WARNINGS - Hypotension, and PRECAUTIONS - Drug Interactions).

Concomitant Diuretic Therapy

In patients receiving diuretics, COZAAR® therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of COZAAR®, to reduce the likelihood of hypotension (see WARNINGS – Hypotension, and PRECAUTIONS – Drug Interactions). If this is not possible because of the patient's condition, COZAAR® should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Dosage in the Elderly

No initial dosage adjustment is necessary for most elderly patients. However, appropriate monitoring of these patients is recommended.

Renal Impairment

No initial dosage adjustment is usually necessary for patients with renal impairment, including those requiring hemodialysis. However, appropriate monitoring of these patients is recommended.

Hepatic Impairment

An initial dosage of 25 mg should be considered for patients with hepatic impairment, or a history of hepatic impairment (see PRECAUTIONS - Patients with Impaired Liver Function, and PHARMACOLOGY).

COMPOSITION

COZAAR® is supplied as unscored film-coated tablets containing either 25 mg, 50 mg, or 100 mg of the active ingredient, losartan potassium. Each tablet contains the following non-medicinal ingredients: microcrystalline cellulose, lactose, corn starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and colouring agents (D&C yellow No. 10 aluminum lake, FD&C blue No. 2 aluminum lake, and titanium dioxide).

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°C - 30°C). Keep container tightly closed. Protect from light.

AVAILABILITY OF DOSAGE FORMS

Tablets COZAAR® 25 mg, are light green, teardrop shaped, unscored, film-coated tablets, with code 951 on one side and MRK on the other. Available in blister packages of 30 tablets.

Tablets COZAAR® 50 mg, are green, teardrop shaped, unscored, film-coated tablets, with code MRK 952 on one side and COZAAR on the other. Available in blister packages of 30 tablets.

Tablets COZAAR® 100 mg, are dark green, teardrop shaped, unscored, film-coated tablets, with code 960 on one side and MRK on the other. Available in blister packages of 30 tablets.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(468-c.2.99)

Reference for 4061a, 4062a

1. MacKay JH et al. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. Arch Intern Med 1996;156:278-85.

4061a, 4062a, 4247a, 4248a

®HYZAAR®

losartan potassium and hydrochlorothiazide

Tablets 50 mg/12.5 mg

Angiotensin II Receptor Antagonist and Diuretic

ACTION AND CLINICAL PHARMACOLOGY

HYZAAR® (losartan potassium and hydrochlorothiazide) combines the actions of losartan potassium, an angiotensin II receptor antagonist, and that of a thiazide diuretic, hydrochlorothiazide.

Losartan

Losartan potassium antagonizes angiotensin II by blocking the angiotensin type one (AT_1) receptor.

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system. Its effects include vasoconstriction and the stimulation of aldosterone secretion by the adrenal cortex.

Losartan, and its active metabolite, E-3174, block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to AT_1 receptors found in many tissues, including vascular smooth muscle. A second type of angiotensin II receptor has been identified as the AT_2 receptor, but it plays no known role in cardiovascular homeostasis to date. Both losartan and its active metabolite do not exhibit any agonist activity at the AT_1 receptor, and have much greater affinity, in the order of 1000-fold, for the AT_1 receptor than for the AT_2 receptor. *In vitro* binding studies indicate that losartan itself is a reversible, competitive antagonist at the AT_1 receptor, while the active metabolite is 10 to 40 times more potent than losartan, and is a reversible, non-competitive antagonist of the AT_1 receptor.

Neither losartan nor its active metabolite inhibits angiotensin converting enzyme (ACE), also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanism of electrolyte reabsorption. It increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure.

Pharmacokinetics

Losartan

Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P-450 enzymes. It is converted, in part, to an active carboxylic acid metabolite, E-3174, that is responsible for most of the angiotensin II receptor antagonism that follows oral losartan administration.

The terminal half-life of losartan itself is about 2 hours, and that of the active metabolite, about 6-9 hours. The pharmacokinetics of losartan and this metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulate in plasma upon repeated once-daily administration.

Following oral administration, losartan is well absorbed, with systemic bioavailability of losartan approximately 33%. About 14% of an orally-administered dose of losartan is converted to the active metabolite, although about 1% of subjects did not convert losartan efficiently to the active metabolite.

Mean peak concentrations of losartan occur at about one hour, and that of its active metabolite at about 3-4 hours. Although maximum plasma concentrations of losartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times greater than that of losartan.

Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Various losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, E-3174, several inactive metabolites are formed. *In vitro* studies indicate that the cytochrome P-450 isoenzymes 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites.

The volume of distribution of losartan is about 34 liters, and that of the active metabolite is about 12 liters.

Total plasma clearance of losartan is about 600 mL/min, with about 75 mL/min accounted for by renal clearance. Total plasma clearance of the active metabolite is about 50 mL/min, with about 25 mL/min accounted for by renal clearance. Both biliary and urinary excretion contribute substantially to the elimination of losartan and its metabolites.

Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma half-life is 5.6-14.8 hours when the plasma levels can be followed for at least 24 hours. At least 61% of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Pharmacodynamics

Losartan

Losartan inhibits the pressor effect of angiotensin II. A dose of 100 mg inhibits this effect by about 85% at peak, with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity, and a consequent rise in angiotensin II plasma concentration, in hypertensive patients.

Maximum blood pressure lowering, following oral administration of a single dose of losartan, as seen in hypertensive patients, occurs at about 6 hours.

In losartan-treated patients during controlled trials, there was no meaningful change in heart rate.

There is no apparent rebound effect after abrupt withdrawal of losartan therapy.

Black hypertensive patients show a smaller average blood pressure response to losartan monotherapy than other hypertensive patients.

Hydrochlorothiazide

Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

Losartan – Hydrochlorothiazide

The components of HYZAAR® have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone.

The antihypertensive effect of HYZAAR® is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of HYZAAR® had no clinically significant effect on heart rate.

INDICATIONS AND CLINICAL USE

HYZAAR® (losartan potassium and hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate.

HYZAAR® is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

Losartan should normally be used in those patients in whom treatment with diuretic or beta blocker was found ineffective or has been associated with unacceptable adverse effects.

CONTRAINDICATIONS

HYZAAR® (losartan potassium and hydrochlorothiazide) is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, it is also contraindicated in patients with anuria, and in patients who are hypersensitive to other sulfonamide-derived drugs.

WARNINGS

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, HYZAAR® (losartan potassium and hydrochlorothiazide) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of losartan potassium as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, losartan potassium should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as means of reversing hypotension and/or substituting for impaired renal function. Neither losartan nor the active metabolite can be removed by hemodialysis.

Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard including fetal or neonatal jaundice, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Animal data: Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, which include decreased body weight, mortality and/or renal toxicity. Significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of losartan, in some cases after the first dose. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

Azotemia

Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the diuretic should be discontinued.

Hypersensitivity Reactions

Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

PRECAUTIONS

Renal Impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal functions have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

Use of losartan should include appropriate assessment of renal function.

Thiazides should be used with caution.

Because of the hydrochlorothiazide component, HYZAAR® (losartan potassium and hydrochlorothiazide) is not recommended in patients with severe renal impairment (creatinine clearance ≤30 mL/min).

Patients with Liver Impairment
Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan and its active metabolite in cirrhotic patients after administration of COZAAR® (losartan potassium), a lower dose should be considered for patients with hepatic impairment, or a history of hepatic impairment (see DOSAGE AND ADMINISTRATION, and PHARMACOLOGY).

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Metabolism
Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol, triglyceride and glucose levels may be associated with thiazide diuretic therapy.

Valvular Stenosis
There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Use in Nursing Mothers
It is not known whether losartan or its active metabolite are excreted in human milk, however significant levels of both of these compounds have been shown to be present in the milk of lactating rats. Thiazides appear in human milk. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children
HYZAAR® has not been studied in children, therefore use in this age group is not recommended.

Use in the Elderly
No overall differences in safety were observed between elderly patients and younger patients, but appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population.

DRUG INTERACTIONS

Diuretics
Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with losartan potassium. The possibility of symptomatic hypotension with losartan potassium can be minimized by discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with losartan potassium (see WARNINGS – Hypotension, and DOSAGE AND ADMINISTRATION).

Agents Increasing Serum Potassium
Since losartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium when losartan therapy is instituted. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that losartan may have on serum potassium.

Lithium Salts
As with other drugs which eliminate sodium, lithium clearance may be reduced in the presence of losartan. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered with losartan.

Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Digitalis
In 9 healthy volunteers, when a single oral dose of 0.5 mg digoxin was administered to patients receiving losartan for 11 days, digoxin AUC and digoxin C_{max} ratios, relative to placebo, were found to be 1.06 (90% C.I. 0.98 - 1.14) and 1.12 (90% C.I. 0.97 - 1.28), respectively. The effect of losartan on steady-state pharmacokinetics of cardiac glycosides is not known.

Thiazide-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias.

Warfarin
Losartan administered for 7 days did not affect the pharmacokinetics or pharmacodynamic activity of a single dose of warfarin. The effect of losartan on steady-state pharmacokinetics of warfarin is not known.

Drugs Affecting Cytochrome P-450 System
When losartan was administered to 10 healthy male volunteers as a single dose in steady-state conditions of phenobarbital, a cytochrome P-450 inducer, losartan AUC, relative to baseline, was 0.80 (90% C.I. 0.72 - 0.88), while AUC of the active metabolite, E-3174, was 0.80 (90% C.I. 0.78 - 0.82).

When losartan was administered to 8 healthy male volunteers as a single dose in steady-state conditions of cimetidine, a cytochrome P-450 inhibitor, losartan AUC, relative to baseline, was 1.18 (90% C.I. 1.10 - 1.27), while AUC of the active metabolite, E-3174, was 1.00 (90% C.I. 0.92 - 1.08).

d-Tubocurarine
Thiazide drugs may increase the responsiveness to tubocurarine.

Insulin
Insulin requirements in diabetic patients treated with diuretics may be increased, decreased or unchanged. Diabetes mellitus which has been latent may become manifest during thiazide administration.

Alcohol, Barbiturates, or Narcotics
Diuretic potentiation of orthostatic hypotension may occur.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia, may occur when given concomitantly with diuretics.

Pressor Amines (e.g. norepinephrine)
In the presence of diuretics possible decreased response to pressor amines may be seen but not sufficient to preclude their use.

Non Steroidal Anti-inflammatory Drugs
In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when HYZAAR® and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

ADVERSE REACTIONS

HYZAAR® (losartan potassium and hydrochlorothiazide) has been evaluated for safety in 2498 patients treated for essential hypertension. Of these, 1088 were treated with HYZAAR® monotherapy in controlled clinical trials. In open studies, 926 patients were treated with HYZAAR® for a year or more.

The following potentially serious adverse reactions have been reported rarely with HYZAAR® in controlled clinical trials: syncope, hypotension.

In controlled clinical trials, discontinuations of therapy due to clinical adverse experiences occurred in 2.4% and 2.1% of patients treated with HYZAAR® and placebo, respectively.

In double-blind controlled clinical trials, the following adverse experiences were reported with losartan potassium - hydrochlorothiazide in ≥1% of patients, regardless of drug relationship:

	Losartan Potassium – Hydrochlorothiazide (n=1088)	Losartan Alone (n=655)	Hydrochlorothiazide (n=272)	Placebo (n=187)
Body as a Whole				
Abdominal pain	1.3	0.9	1.8	1.1
Asthenia/fatigue	3.1	2.9	5.1	3.7
Edema/swelling	1.2	0.6	2.9	1.6
Cardiovascular				
Palpitation	1.6	1.5	1.1	0
Digestive				
Diarrhea	1.6	1.8	0.4	2.1
Nausea	1.5	1.2	0	2.1
Musculoskeletal				
Back pain	2.9	1.1	0	0.5
Nervous/Psychiatric				
Dizziness	5.8	3.7	3.7	3.2
Headache	8.0	10.5	14.0	15.0
Respiratory				
Bronchitis	1.1	1.2	0.4	1.6
Cough	2.2	2.1	1.1	2.1
Influenza	1.2	0.2	0.7	0.5
Pharyngitis	1.2	0.8	1.8	1.6
Sinusitis	1.0	0.9	2.2	0.5
Upper respiratory infection	5.8	4.6	5.5	4.8
Skin				
Rash	1.3	0.5	1.5	0.5

In these controlled clinical trials, dizziness was the only adverse experience, occurring in more than 1% of cases, that was reported as drug-related, and that occurred at a greater incidence in losartan potassium - hydrochlorothiazide-treated (3.3%) than placebo-treated (2.1%) patients.

Thrombocytopenia and Adult Respiratory Distress Syndrome have been reported rarely in post-marketing experience.

In double-blind, controlled clinical trials with losartan potassium alone, the following adverse experiences were reported at an occurrence rate of less than 1%, regardless of drug relationship: orthostatic effects, somnolence, vertigo, epistaxis, tinnitus, constipation, malaise, rash.

Other adverse experiences reported with losartan potassium alone in open-label studies or post marketing use, regardless of drug relationship, include diarrhea, migraine, myalgia, pruritus, taste disorder, and urticaria.

Angioedema (involving swelling of the face, lips, and/or tongue), has been reported rarely in post-marketing experience with losartan potassium.

LABORATORY TEST FINDINGS

Liver Function Tests: Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Hyperkalemia: In controlled hypertensive trials with losartan monotherapy and HYZAAR®, a serum potassium > 5.5 mEq/L occurred in 1.5% and 0.7% of patients, respectively. However, no patient discontinued losartan or HYZAAR® therapy due to hyperkalemia.

Serum Creatinine, Blood Urea Nitrogen (BUN): Minor increases in blood urea nitrogen (1.0%) and serum creatinine (1.0%) were observed in patients with essential hypertension treated with HYZAAR®. More marked increases have also been reported and were more likely to occur in patients with bilateral renal artery stenosis (see PRECAUTIONS).

Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with losartan potassium alone. In clinical studies, no patient discontinued taking losartan potassium alone due to increased BUN or serum creatinine.

No other adverse experiences have been reported with HYZAAR® which have not been reported with losartan or hydrochlorothiazide individually.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific information is available on the treatment of overdosage with HYZAAR® (losartan potassium and hydrochlorothiazide). Treatment is symptomatic and supportive.

Losartan
Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. The fixed combination is not for initial therapy. The dose of HYZAAR® (losartan potassium and hydrochlorothiazide) should be determined by the titration of the individual components.

Once the patient has been stabilized on the individual components as described below, either one HYZAAR® 50/12.5 mg tablet or two tablets once daily may be substituted if the doses on which the patient was stabilized are the same as those in the fixed combination (see INDICATIONS AND CLINICAL USE).

HYZAAR® may be administered with or without food, however it should be taken consistently with respect to food intake.

Losartan Monotherapy
The usual starting dose of losartan monotherapy is 50 mg once daily.

Dosage should be adjusted according to blood pressure response. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy.

The usual dose range for losartan is 50 to 100 mg once daily. A dose of 100 mg daily should not be exceeded, as no additional antihypertensive effect is obtained with higher doses.

In most patients taking losartan 50 mg once daily, the antihypertensive effect is maintained. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. This can be evaluated by measuring the blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dosage, or an increase in the dose should be considered. If blood pressure is not adequately controlled with losartan alone, a non-potassium-sparing diuretic may be administered concomitantly.

For patients with volume-depletion, a starting dose of 25 mg once daily should be considered (see WARNINGS – Hypotension, and PRECAUTIONS – Drug Interactions).

Diuretic Treated Patients
In patients receiving diuretics, losartan therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of losartan, to reduce the likelihood of hypotension (see WARNINGS – Hypotension, and PRECAUTIONS – Drug Interactions). If this is not possible because of the patient's condition, losartan should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Dosage Adjustment in Renal Impairment
No initial dosage adjustment in losartan is usually necessary for patients with renal impairment, including those requiring hemodialysis. However, appropriate monitoring of these patients is recommended.

The usual regimens of therapy with HYZAAR® may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so HYZAAR® is not recommended.

Patients with Liver Impairment
Since dosage adjustment of losartan is required in patients with liver impairment, and thiazide diuretics may precipitate hepatic coma, a fixed combination product such as HYZAAR® is not advisable (see PRECAUTIONS - Patients with Liver Impairment).

Elderly Patients
No initial dosage adjustment is necessary for most elderly patients. Appropriate caution should nevertheless be used when prescribing to the elderly, as increased vulnerability to drug effect is possible in this patient population (see PRECAUTIONS – Use in the Elderly).

COMPOSITION

HYZAAR® is supplied as yellow, teardrop-shaped, film-coated tablets containing 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide, as the active ingredients. Each tablet contains the following non-medicinal ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose hydrous, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and colouring agents (D&C yellow No. 10 aluminum lake, and titanium dioxide). HYZAAR® also contains 4.24 mg (0.108 mEq) of potassium.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°C - 30°C). Keep container tightly closed.

AVAILABILITY OF DOSAGE FORMS

Tablets HYZAAR® 50 mg/12.5 mg, are yellow, teardrop shaped, film-coated tablets, with code MRK 717 on one side and HYZAAR on the other. Available in push-through blister packages of 30 tablets.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(467-b,3.99)

Reference for 4061a, 4062a

1. MacKay JH et al. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. Arch Intern Med 1996;156:278-85.

4061a, 4062a, 4247a, 4248a

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ONCE - DAILY

EFFEXOR® XR

Venlafaxine HCl Extended Release Capsules

EFFEXOR® (venlafaxine hydrochloride) Tablets
EFFEXOR® XR (venlafaxine hydrochloride) Extended Release Capsules

THERAPEUTIC CLASSIFICATION
ANTIDEPRESSANT

ACTIONS AND CLINICAL PHARMACOLOGY

Venlafaxine is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents.

The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its major 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 of 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, with peak plasma concentrations with EFFEXOR® Tablets occurring approximately 2 hours after dosing. Venlafaxine is extensively metabolized, with O-desmethylvenlafaxine, (ODV, the only major active metabolite) peak plasma levels occurring approximately 4 hours after dosing. Following single doses of 25 to 75 mg, mean (± SD) peak plasma concentrations of venlafaxine range from 37 ± 14 to 102 ± 41 ng/mL, respectively, and are reached in 2 ± 1 hours, and mean peak ODV plasma concentrations range from 61 ± 13 to 168 ± 37 ng/mL and are reached in 4 ± 2 hours. Approximately 87% of a single dose of venlafaxine 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%), and 92% of the radioactive dose is recovered within 72 hours. Therefore, renal elimination of venlafaxine and its metabolites is the primary route of excretion.

After administration of EFFEXOR® XR (extended release capsules), the peak plasma concentrations of venlafaxine and ODV are attained within 6.0±1.5 and 8.8±2.2 hours, respectively. The rate of absorption of venlafaxine from the EFFEXOR® XR capsule is slower than its rate of elimination. Therefore, the apparent elimination half-life of venlafaxine following administration of EFFEXOR® XR (15±6 hours) is actually the absorption half-life instead of the true disposition half-life (5±2) hours observed following administration of an EFFEXOR® (venlafaxine hydrochloride) immediate release tablet.

Multiple-Dose Pharmacokinetic Profile (Tablets and Extended Release Capsules)

Steady-state concentrations of both venlafaxine and ODV in plasma are attained within 3 days of oral multiple dose therapy. The clearance of venlafaxine is slightly (15%) lower following multiple doses than following a single dose.

Venlafaxine and ODV exhibited approximately linear kinetics over the dose range of 75 to 450 mg/day.

The mean±SD steady-state plasma clearances of venlafaxine and ODV are 1.3±0.6 and 0.4±0.2 L/hr/kg, respectively; apparent elimination half-life is 5±2 and 11±2 hours, respectively; and apparent (steady-state) volume of distribution is 7.5±3.7 and 5.7±1.8 L/kg, respectively.

Venlafaxine and ODV renal clearances are 49±27 and 94±56 mL/hr/kg, respectively, which correspond to 5±3.0% and 25±13% of an administered venlafaxine dose recovered in urine as venlafaxine and ODV, respectively.

When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended release capsule, the exposure (AUC, area under the concentration curve) to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower following treatment with the extended release capsule. Therefore, the EFFEXOR® XR capsules provide a slower rate of absorption, but the same extent of absorption (i.e., AUC), as the venlafaxine immediate release tablet.

Venlafaxine and ODV are 27 and 30% bound to human plasma proteins, respectively. Therefore, administration of venlafaxine to a patient taking another drug that is highly protein-bound should not cause increased free concentrations of the other drug. Following intravenous administration, the steady-state volume of distribution of venlafaxine is 4.4±1.9 L/kg, indicating that venlafaxine distributes well beyond the total body water.

Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver. On the basis of mass balance studies, at least 92% of a single dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is approximately 45%. The primary metabolite of venlafaxine is ODV, which is an active metabolite. Venlafaxine is also metabolized to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of ODV is catalysed by CYP2D6 and that the formation of N-desmethylvenlafaxine is catalysed by CYP3A3/4. The results of the *in vitro* studies have been confirmed in a clinical study with subjects who are CYP2D6 poor and extensive metabolizers. However, despite the metabolic differences between the CYP2D6 poor and extensive metabolizers, the total exposure to the sum of the two active species (venlafaxine and ODV, which have comparable activity) was similar in the two metabolizer groups.

Food has no significant effect on the absorption of venlafaxine or on the subsequent formation of ODV.

Age and Gender

Population pharmacokinetic analyses of 547 venlafaxine-treated patients from three studies involving both venlafaxine immediate release tablets and venlafaxine extended release capsules showed that age and sex do not significantly affect the pharmacokinetics of venlafaxine. A 20% reduction in clearance was noted for ODV in subjects over 60 years old; this was possibly caused by the decrease in renal function that typically occurs with aging. Dosage adjustment based upon age or gender is generally not necessary (See **Dosage and Administration**).

Extensive/Poor Metabolizers

Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, there is no need for different venlafaxine dosing regimens for these two groups.

Hepatic Disease

In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV were significantly altered. Venlafaxine elimination half-life was prolonged by about 30%, and clearance was 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 patients with liver disease (See DOSAGE AND ADMINISTRATION).**

Renal Disease

In patients with moderate to severe impairment of renal function (GFR = 10-70 mL/min), venlafaxine elimination half-life was prolonged by 50%, and clearance was deceased by about 24% compared to normal subjects. ODV elimination half-life was prolonged by about 40%, but clearance was unchanged.

In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was decreased by about 57%. In dialysis patients, ODV elimination half-life was prolonged by about 142%, and clearance was reduced by about 56% compared to normal subjects. A large degree of intersubject variability was noted.

Dosage adjustment is necessary in patients with renal disease (SEE DOSAGE AND ADMINISTRATION).

Clinical Trials

The efficacy of EFFEXOR® tablets in the treatment of depression was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-II 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.

The efficacy of EFFEXOR® XR (venlafaxine hydrochloride extended release) capsules as a treatment for depression was established in two placebo-controlled, short-term, flexible-dose studies in adult outpatients meeting DSM-III-R or DSM-IV criteria for major depression. An 8-week study utilizing EFFEXOR® XR doses in a range 75-225 mg/day (mean dose for completers was 177 mg/day) and a 12-week study utilizing EFFEXOR® XR doses in a range 75-150 mg/day (Mean dose for completers was 136 mg/day) both demonstrated superiority of EFFEXOR® XR over placebo on the HAM-D total score, the HAM-D Depressed Mood item, the MADRS total score, the CGI Severity of Illness scale, and the CGI Global Improvement scale. In both studies, EFFEXOR® XR was also significantly better than placebo for certain factors of the HAM-D, including the anxiety/somatization factor, the cognitive disturbance factor, and the retardation factor, as well as for the psychic anxiety score.

INDICATIONS AND CLINICAL USE

EFFEXOR®/EFFEXOR® XR (venlafaxine HCl) Tablets/Capsules are indicated for the symptomatic relief of depressive illness.

The effectiveness of EFFEXOR® in long-term use (i.e. for more than 4-6 weeks - immediate release tablets, or 8-12 weeks - extended release capsules) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use EFFEXOR® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

EFFEXOR®/EFFEXOR® XR (venlafaxine HCl) Tablets/Capsules are contraindicated in patients with known hypersensitivity to venlafaxine or to any of the components of the formulations.

Monoamine Oxidase Inhibitors (MAOI's): There have been reports of serious, sometimes fatal reactions in patients receiving antidepressants with pharmacological properties similar to those of EFFEXOR®/EFFEXOR® XR in combination with a MAOI. Therefore, EFFEXOR®/EFFEXOR® XR should not be used in combination with MAOIs or within two weeks of terminating treatment with MAOIs. Treatment with MAOIs should not be started until 2 weeks after discontinuation of EFFEXOR®/EFFEXOR® XR therapy.

WARNINGS

Sustained Hypertension

Treatment with EFFEXOR® (venlafaxine HCl) Tablets was associated with modest but sustained increases in blood pressure during premarketing studies. Sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg **and** ≥ 10 mm Hg above baseline for 3 consecutive visits, showed the following incidence and dose-relationship:

	Probability of Sustained Elevation in SDBP (Pool of Premarketing Studies with EFFEXOR®/EFFEXOR® XR)	
Treatment Group	**Incidence of Sustained Elevation in SDBP (%)**	
Venlafaxine	Immediate Release	Extended Release
< 100 mg/day	2	3
101-200 mg/day	5	2
201-300 mg/day	6	4
> 300 mg/day	13	NE*
Placebo	2	NE*

*Not evaluable

An analysis of the blood pressure increases in patients with sustained hypertension and in the 19 patients who were discontinued from treatment because of hypertension (<1% of total venlafaxine-treated group) showed that most of the blood pressure increases were in the range of 10 to 15 mm Hg, SDBP.

In placebo-controlled premarketing depression studies with EFFEXOR® XR, a final on-therapy mean increase in supine diastolic pressure (SDBP) of < 1.2 mm Hg was observed for EFFEXOR® XR-treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. Less than 3% of EFFEXOR® XR patients treated with doses of 75 to 300 mg/day had sustained elevations in blood pressure (defined as treatment-emergent SDBP ≥ 90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits). An insufficient number of patients received doses of EFFEXOR® XR > 300 mg/day to evaluate systematically sustained blood pressure increases. Less than 1% of EFFEXOR® XR-treated patients in double-blind, placebo-controlled premarketing depression studies discontinued treatment because of elevated blood pressure compared with 0.4% of placebo-treated patients.

Sustained increases could have adverse consequences. Therefore, it is recommended that patients receiving venlafaxine have their blood pressure monitored regularly. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered after a benefit-risk assessment is made.

PRECAUTIONS

General

Suicide

The possibility of a suicide attempt in seriously depressed patients is inherent to the illness and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization. In order to reduce the risk of overdose, prescriptions for EFFEXOR®/EFFEXOR® XR (venlafaxine HCl) Tablets/Capsules should be written for the smallest quantity of tablets/capsules consistent with good patient management.

Seizures

During premarketing testing, seizures were reported in 8 out of 3,082 EFFEXOR® *Tablet*-treated patients (0.26%). In 5 of the 8 cases with immediate release tablets, patients were receiving doses of 150 mg/day or less. No seizures were seen in 705 EFFEXOR® XR *Capsule*-treated patients. However, patients with a history of convulsive disorders were excluded from most of these studies. EFFEXOR®/EFFEXOR® XR should be used cautiously in patients with a history of seizures, and should be promptly discontinued in any patient who develops seizures.

Activation of Mania/Hypomania

During Phase II and III trials, mania or hypomania occurred in 0.5% of EFFEXOR® *Tablet*-treated patients and in 0.3% of EFFEXOR® XR *Capsule*-treated patients. Mania or hypomania occurred in 0.8% of all venlafaxine-treated patients. Mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, EFFEXOR®/EFFEXOR® XR should be used cautiously in patients with a history of mania.

Use in Patients with Concomitant Illness

Clinical experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering venlafaxine to patients with diseases or conditions that could affect hemodynamic responses or metabolism. Patients should be questioned about any prescription or "over the counter drugs" that they are taking, or planning to take, since there is a potential for interactions.

- **Cardiac Disease**

  Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's clinical trials.

  Evaluation of the electrocardiograms for 769 patients who received venlafaxine *immediate release tablets* in 4- to 6-week double-blind trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo.

  The electrocardiograms for 357 patients who received EFFEXOR® XR and 285 patients who received placebo in 8 to 12 week double-blind, placebo-controlled trials were analyzed. The mean change from baseline in corrected QT interval (QTc) for EFFEXOR® XR-treated patients was increased relative to that for placebo-treated patients (increase of 4.7 msec for EFFEXOR® XR and decrease of 1.9 msec for placebo). Three of 705 EFFEXOR® XR-treated patients in phase III studies experienced QTc prolongation to 500 msec during treatment. Baseline QTc was > 450 msec for all 3 patients. No case of sudden unexplained death or serious ventricular arrhythmia, which are possible clinical sequelae of QTc prolongation, was reported in EFFEXOR® XR pre-marketing studies.

  The mean heart rate was increased by about 4 beats per minute during treatment with EFFEXOR® and EFFEXOR® XR. Venlafaxine treatment has been associated with sustained hypertension **(see WARNINGS)**.

- **Hepatic and Renal Disease**

  In patients with hepatic or renal impairment (GFR=10-70 mL/min), the pharmacokinetic disposition of both venlafaxine and ODV are significantly altered. **Dosage adjustment is necessary in these patients (See DOSAGE AND ADMINISTRATION).**

Insomnia and Nervousness

Treatment-emergent insomnia and nervousness were more commonly reported for patients treated with EFFEXOR® and EFFEXOR® XR than with placebo (see **ADVERSE REACTIONS**).

Changes in Appetite and Weight

Treatment-emergent anorexia was more commonly reported for EFFEXOR® and EFFEXOR® XR-treated than placebo-treated patients (see ADVERSE EFFECTS). Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment.

Interference with Cognitive and Motor Performance

Clinical studies were performed to examine the effects of venlafaxine on behavioral performance of healthy individuals. The results revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, since any psychoactive drug may impair judgement, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Use in Pregnancy, Labour and Delivery

There are no adequate and well controlled studies with venlafaxine in pregnant women. Therefore, venlafaxine should only be used during pregnancy if clearly needed. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Use in Nursing Mothers

It is not known whether venlafaxine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, lactating women should not nurse their infants while receiving venlafaxine.

Paediatric Use

Safety and efficacy in children below the age of 18 have not been established.

Use in the Elderly

Of the 2,897 patients in Phase II and III trials with EFFEXOR® Tablets, 357 (12%) were 65 years of age or older. Forty three (43%) of the patients in trials with EFFEXOR® XR Capsules, were 65 years of age or older. No overall differences in effectiveness and safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

Discontinuation Symptoms

While the discontinuation effects of EFFEXOR® have not been systematically evaluated in controlled clinical trials, a retrospective survey of new events occurring during taper or following discontinuation revealed the following six events that occurred at an incidence of at least 5%, and for which the incidence for EFFEXOR® was at least twice the placebo incidence: asthenia, dizziness, headache, insomnia, nausea and nervousness.

With EFFEXOR® XR, the following six events occurred with an incidence of at least 3%, and for which the incidence of EFFEXOR® XR was at least twice the placebo incidence: dizziness, dry mouth, insomnia, nausea, nervousness and sweating.

Therefore, it is recommended that the dosage be tapered gradually and the patient monitored (**See DOSAGE AND ADMINISTRATION**).

Drug Interactions

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

- ***Lithium***

  The steady-state pharmacokinetics of venlafaxine administered as 50 mg every 8 hours was not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. Venlafaxine had no effect on the pharmacokinetics of lithium.

- ***Diazepam***

  The steady-state pharmacokinetics of venlafaxine administered as 50 mg every 8 hours was not affected when a single 10 mg oral dose of diazepam was administered to 18 healthy male subjects. Venlafaxine had no effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam. Additionally, venlafaxine administration did not affect the psychomotor and psychometric effects induced by diazepam.

- ***Cimetidine***

  Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs in 18 healthy male subjects resulted in inhibition of first-pass metabolism of venlafaxine. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (C_{max}) of the drug were increased by about 60%. However, there was no effect on the pharmacokinetics of ODV. The overall pharmacological activity of venlafaxine plus ODV is expected to increase only slightly, and no dosage adjustment should be necessary for most normal adults.

  However, for patients with pre-existing hypertension, for elderly patients and for patients with hepatic or renal dysfunction, the interaction associated with the concomitant use of cimetidine and venlafaxine is not known and potentially could be more pronounced. Therefore, caution is advised with such patients.

- ***Haloperidol***

  Venlafaxine administered under steady-state conditions at 150 mg/day in 24 healthy subjects decreased total oral-dose clearance (Cl/F) of a single 2 mg dose of haloperidol by 42%, which resulted in a 70% increase in haloperidol AUC. In addition, the haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life ($T_{1/2}$) was unchanged. The mechanism explaining this finding is unknown.

- ***Imipramine***

  Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, AUC, C_{max} and C_{min} of desipramine (the active metabolite of imipramine) increased by approximately 35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by at least 2.5 fold (with venlafaxine 37.5 mg q12h) and by 4.5 fold (with venlafaxine 75 mg q12h). The clinical significance of elevated 2-OH-desipramine levels is unknown.

  Imipramine partially inhibited the CYP2D6-mediated formation of ODV. However, the total concentration of active compounds (venlafaxine plus ODV) was not affected by coadministration with imipramine, and no dosage adjustment is required.

- ***Risperidone***

  Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxyrisperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).

- ***Drugs Highly Bound to Plasma Proteins***

  Venlafaxine is not highly bound to plasma proteins; therefore, administration of venlafaxine to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.

- ***Drugs that Inhibit Cytochrome P450 Isoenzymes***

  CYP2D6-Inhibitors:

  In vitro and *in vivo* studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6 mediated metabolism and venlafaxine. Drug interactions that reduce the metabolism of venlafaxine to ODV (see **Imipramine** above) potentially increase the plasma concentrations of venlafaxine and lower the concentrations of the active metabolite. However, the pharmacokinetic profile of venlafaxine in subjects concomitantly receiving a CYP2D6-inhibitor would not be substantially different than the pharmacokinetic profile in subjects who are CYP2D6 poor metabolizers, and no dosage adjustment is required.

  CYP3A3/4 Inhibitors:

  In vitro studies indicate that venlafaxine is likely metabolized to a minor, less active metabolite, N-desmethylvenlafaxine, by CYP3A3/4. Because CYP3A3/4 is typically a minor pathway relative to CYP2D6 in the metabolism of venlafaxine, the potential for a clinically significant drug interaction between drugs that inhibit CYP3A3/4-mediated metabolism and venlafaxine is small. However, because the two primary metabolic pathways for venlafaxine are through CYP2D6 and, to a lesser extent, CYP3A3/4, concomitant intake of inhibitors of both of these isoenzymes is not recommended during treatment with venlafaxine. However, interactions between concomitant intake of inhibitors of both CYP2D6 and CYP3A3/4 with venlafaxine has not been studied.

- ***Drugs Metabolized by Cytochrome P450 Isoenzymes***

  CYP2D6

  In vitro studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. These findings have been confirmed *in vivo* by a clinical drug interaction study comparing the effect of venlafaxine with that of fluoxetine on the CYP2D6-mediated metabolism of dextromethorphan to dextrorphan.

  CYP3A4

  Venlafaxine did not inhibit CYP3A4 *in vitro*. This finding was confirmed *in vivo* by clinical drug interaction studies in which venlafaxine did not inhibit the metabolism of several CYP3A4 substrates, including alprazolam, diazepam, and terfenadine.

  CYP1A2

  Venlafaxine did not inhibit CYP1A2 *in vitro*. This finding was confirmed *in vivo* by a clinical drug interaction study in which venlafaxine did not inhibit the metabolism of caffeine, a CYP1A2 substrate.

  CYP2C9

  Venlafaxine did not inhibit CYP2D9 *in vitro*. The clinical significance of this finding is unknown.

  CYP2C19

  Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see Diazepam above).

- ***Monoamine Oxidase Inhibitors:*** *See "Contraindications".*

- ***Other CNS-Active Drugs***

  The risk of using venlafaxine in combination with other CNS-active drugs (including alcohol) has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.

Electroconvulsive Therapy

There are no clinical data on the use of electroconvulsive therapy combined with EFFEXOR® or EFFEXOR® XR treatment.

Drug Abuse and Dependence

Physical and Psychological Dependence

In vitro studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. It has no significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

While EFFEXOR®/EFFEXOR® XR have not been systematically studied in clinical trials for their potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behaviour).

ADVERSE REACTIONS

Commonly Observed Adverse Reactions

The most commonly observed adverse events associated with the use of EFFEXOR® and EFFEXOR® XR (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., incidence for EFFEXOR®/EFFEXOR® XR at least twice that for placebo), derived from the 2% incidence Table 2, were:

EFFEXOR® : asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision, and abnormal ejaculation/orgasm and impotence in men.

EFFEXOR® XR: abnormal dreams, anorexia, dizziness, dry mouth, nausea, nervousness, somnolence, sweating, and tremor as well as abnormal ejaculation/orgasm in men.

Adverse Reactions Associated with Discontinuation of Treatment

Nineteen percent (537/2897) of EFFEXOR® and 12% (88/705) of EFFEXOR® XR-treated patients in Phase II and III depression studies discontinued treatment due to an adverse reaction. The more common events (≥ 1%) associated with discontinuation of treatment and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) are shown in Table 1.

TABLE 1: ADVERSE REACTIONS ASSOCIATED WITH DISCONTINUATION OF TREATMENT

	EFFEXOR® (n = 2897)	Placebo (n = 609)	EFFEXOR® XR (n = 705)	Placebo (n = 285)
CNS				
Somnolence	3%	1%	2%	-
Insomnia	3%	1%	-	-
Dizziness	3%	-	#	@
Nervousness	2%	-	-	@
Dry Mouth	2%	-	-	-
Anxiety	2%	1%	-	-
Gastrointestinal				
Nausea	6%	1%	4%	-
Anorexia	1%	-	1%	-
Urogenital				
Abnormal Ejaculation*	3%	-	-	-
Other				
Headache	3%	1%	#	@
Asthenia	2%	-	-	@
Sweating	2%	-	-	-

*: percentages based on the number of males.
-: Less than 1%
#: greater than 1% but active drug rate not twice rate for placebo.
@: 1% or greater

Incidence in Controlled Trials

The table that follows (Table 2) enumerates adverse events that occurred at an incidence of 2% or more, and were more frequent than in the placebo group, among venlafaxine-treated patients.

EFFEXOR®: patients participated in 4- to 8- week placebo-controlled trials in which doses in the range of 75 to 375 mg/ day were administered.

EFFEXOR® XR: patients participated in 8- to 12-week placebo-controlled trials in which doses in the range of 75 to 225 mg/ day were administered.

Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that the cited frequencies for EFFEXOR® XR cannot be compared with figures obtained from other clinical investigations of EFFEXOR® which involved different treatments, uses and investigators. The cited figures for EFFEXOR® XR, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

TABLE 2: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS (PERCENTAGE)[1]

	EFFEXOR® (n = 1033)	Placebo (n = 609)	EFFEXOR® XR (n = 357)	Placebo (n = 285)
Body System Preferred Term				
Body as a whole				
Headache	25	24	#	@
Asthenia	12	6	8	7
Infection	6	5	#	@
Chills	3	-	-	-
Cardiovascular				
Vasodilation	4	3	4	2
Increased blood pressure/hypertension	2	-	4	-
Tachycardia	2	-	-	-
Dermatological				
Sweating	12	3	14	3
Rash	3	2	-	-
Gastrointestinal				
Nausea	37	11	31	12
Constipation	15	7	8	5
Anorexia	11	2	8	4
Diarrhoea	8	7	#	@
Vomiting	6	2	4	2
Dyspepsia	5	4	#	@
Flatulence	3	2	4	3
Metabolic				
Weight loss	#	-	3	-
Nervous				
Somnolence	23	9	17	8
Dry mouth	22	11	12	6
Dizziness	19	7	20	9
Insomnia	18	10	17	11
Nervousness	13	6	10	5
Anxiety	6	3	#	@
Tremor	5	-	5	2
Abnormal Dreams	4	3	7	2
Hypertonia	3	-	-	-
Paraesthesia	3	-	3	-
Libido decreased	2	-	3	-
Agitation	2	-	3	-
Depression	-	-	3	-
Respiration				
Pharyngitis	#	#	7	6
Yawn	3	-	3	-
Special Senses				
Abnormal vision	6	2	4	-
Taste perversion	2	-	-	-
Urogenital system				
Abnormal ejaculation /orgasm	12[2]	-[2]	16[2]	-[2]
Impotence	6[2]	-[2]	4[2]	-[2]
Anorgasmia	-[2]	-[2]	3[2]	-[2]
Urinary frequency	3	-	-	-
Urination impaired	2	-	-	-

[1] Events reported by at least 2% of patients treated with EFFEXOR®/EFFEXOR® XR are included, and are rounded to the nearest %. Events for which the EFFEXOR®/EFFEXOR® XR incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhoea,[2] dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis and sinusitis.

[2] Incidence based on number of male patients.

[3] Incidence based on number of female patients.

- Incidence less than 2%.
Incidence greater than 2%, but active drug incidence less than incidence for placebo.
@ Incidence 2% or greater

Dose Dependency of Adverse Events

A comparison of adverse event rates in a fixed-dose study comparing EFFEXOR® Tablets 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with EFFEXOR® use, as shown in the table that follows (Table 3). The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one EFFEXOR® group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value ≤ 0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

TABLE 3: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN A DOSE COMPARISON TRIAL

	EFFEXOR® Tablets (mg/day)			
Body System Preferred Term	**Placebo (n = 92)**	**75 (n = 89)**	**225 (n = 89)**	**375 (n = 88)**
Body as a Whole				
Abdominal pain	3.3%	3.4%	2.2%	8.0%
Asthenia	3.3%	16.9%	14.6%	14.8%
Chills	1.1%	2.2%	5.6%	6.8%
Infection	2.2%	2.2%	5.6%	2.3%
Cardiovascular				
Hypertension	1.1%	1.1%	2.2%	4.5%
Vasodilatation	0.0%	4.5%	5.6%	2.3%
Digestive System				
Anorexia	2.2%	14.6%	13.5%	17.0%
Dyspepsia	2.2%	6.7%	6.7%	4.5%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Nervous				
Agitation	0.0%	1.1%	2.2%	4.5%
Anxiety	4.3%	11.2%	4.5%	2.3%
Dizziness	4.3%	19.1%	22.5%	23.9%
Insomnia	9.8%	22.5%	20.2%	13.6%
Libido decreased	1.1%	2.2%	1.1%	5.7%
Nervousness	4.3%	21.3%	13.5%	12.5%
Somnolence	4.3%	16.9%	18.0%	26.1%
Tremor	0.0%	1.1%	2.2%	10.2%
Respiratory				
Yawn	0.0%	4.5%	5.6%	8.0%
Skin and Appendages				
Sweating	5.4%	6.7%	12.4%	19.3%
Special Senses				
Abnormality of accommodation	0.0%	9.1%	7.9%	5.6%
Urogenital System				
Abnormal ejaculation/orgasm	0.0%	4.5%	2.2%	12.5%
Impotence	0.0%	5.8%	2.1%	3.6%
(number of men)	(n = 63)	(n = 52)	(n = 48)	(n = 56)

Adaptation to Certain Adverse Events

In premarketing experience with EFFEXOR® Tablets over a 6-week period, and EFFEXOR® XR capsules over a 12 week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., dizziness and nausea), but less to other effects (e.g., abnormal ejaculation and dry mouth).

Vital Sign Changes

Treatment with EFFEXOR® Tablets (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 2.5 mm Hg averaged over all dose groups, compared to mean decreases ranging from 0.9 to 3.8 mm Hg for placebo. However, there is a dose dependency for blood pressure increase (**see WARNINGS**).

Treatment with EFFEXOR® XR Capsules for up to 12 weeks in premarketing depression trials was associated with a mean increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 0.9 mm Hg, compared with mean decreases ranging from 0.5 to 1.4 mm Hg for placebo (**see WARNINGS**).

Laboratory Changes

Of the serum chemistry and haematology parameters monitored during clinical trials with EFFEXOR,* a statistically significant difference with placebo was seen only for serum cholesterol, i.e., patients treated with EFFEXOR® had mean increases from baseline of 3 mg/dL. In premarketing placebo-controlled depression trials for up to 12 weeks, EFFEXOR® XR was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL. The serum cholesterol changes induced by venlafaxine are of unknown clinical significance.

ECG Changes

In an analysis of ECGs obtained in 769 patients treated with EFFEXOR® Tablets and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, i.e., a mean increase from baseline of 4 beats per minute for EFFEXOR.*

An analysis of ECGs obtained in 357 patients treated with EFFEXOR® XR and 285 patients treated with placebo in controlled clinical trials, revealed a mean increase in corrected QT (QTc) interval relative to placebo (see PRECAUTIONS). A mean increase in heart rate of approximately 4 beats per minute for EFFEXOR® XR compared with 1 beat per minute for placebo was observed.

Other Events Observed During the Premarketing Evaluation of Venlafaxine

During its premarketing assessment, multiple doses of EFFEXOR® XR were administered to 705 patients in phase III depression studies and EFFEXOR® Tablets were administered to 96 patients. In addition, in premarketing assessment of EFFEXOR® Tablets, multiple doses were administered to 2897 patients in phase II-III depression studies. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (EFFEXOR® Tablets only) and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 3698 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 1 and 2, and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it.

Events are further categorized by body system and the frequent adverse events are provided below. Frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing).

Body as a whole – :	chest pain, chills, fever.
Cardiovascular system – :	migraine, postural hypotension, tachycardia.
Digestive system – :	eructation, increased appetite.
Hemic and lymphatic system – :	ecchymosis.
Musculoskeletal system – :	myalgia.
Nervous system – :	amnesia, emotional lability, hypesthesia, sleep disturbance, thinking abnormal, trismus.
Special senses – :	ear pain, taste perversion.
Urogenital system – :	menstrual disorder,* prostatitis,* urinary tract infection, urination impaired, vaginitis.*

*Based on the number of men and women as appropriate.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Human Experience

In postmarketing experience, venlafaxine, taken alone, has not been clearly associated with lethal overdose. However, fatal reactions have been reported in patients taking overdoses of venlafaxine in combination with alcohol and/or other drugs.

EFFEXOR® Tablets

There were 14 reports of acute overdose with EFFEXOR® (venlafaxine HCl), either alone or in combination with other drugs and/or alcohol, among the patients included in the premarketing evaluation. The majority of the reports involved ingestions in which the total dose of EFFEXOR® taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 µg/mL, respectively, and the peak plasma levels of O-desmethyl-venlafaxine were 3.37 and 1.30 µg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

EFFEXOR® XR Capsules

Among the patients included in the premarketing evaluation of venlafaxine extended release capsules, there were 2 reports of acute overdosage with EFFEXOR® XR, either alone or in combination with other drugs. One patient took a combination of 6 g of EFFEXOR® XR and 2.5 mg of lorazepam. This patient was hospitalized, treated symptomatically, and recovered without any untoward effects. The other patient took 2.5 g of EFFEXOR® XR. This patient reported paresthesia of all four limbs but recovered without sequelae.

Overdosage Management

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitoring of cardiac rhythm and vital signs is recommended. General supportive and symptomatic measures are also recommended. Use of activated charcoal, induction of emesis, or gastric lavage should be considered. Due to the large volume of distribution of venlafaxine hydrochloride, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for EFFEXOR®/EFFEXOR® XR are known.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control centre on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

ADULTS:

EFFEXOR® Tablets

The recommended treatment dose is 75 mg per day, administered in two or three divided doses, taken with food. If the expected clinical improvement does not occur after a few weeks, a gradual dose increase to 150 mg/day may be considered. If needed, the dose may be further increased up to 225 mg/day. Increments of up to 75 mg/day should be made at intervals of no less than 4 days. In outpatient settings there was no evidence of the usefulness of doses greater than 225 mg/day for moderately depressed patients. More severely depressed inpatients have responded to higher doses, between 350 and 375 mg/day, given in three divided doses. Maximum: The maximum dose recommended is 375 mg per day (in an inpatient setting).

EFFEXOR® XR Capsules

The recommended dose for venlafaxine ER is 75 mg/day, administered once daily with food, either in the morning or in the evening. Each capsule should be swallowed whole with water. It should not be divided, crushed, chewed, or placed in water. While the relationship between dose and antidepressant response for EFFEXOR® XR has not been adequately explored patients not responding to the initial 75 mg may benefit from dose increases. Depending on tolerability and the need for further clinical effect, the dose should be increased by up to 75 mg/day up to a maximum of 225 mg/day for moderately depressed outpatients. Dose increments should be made at intervals of approximately 2 weeks or more, but not less than 4 days. There is very limited experience with EFFEXOR® XR at doses higher than 225 mg/day, or in severely depressed inpatients.

It should be noted that, while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day for EFFEXOR® Tablets, more severely depressed inpatients responded to a mean dose of 350 mg/day (range of 150 to 375 mg/day).

Switching Patients from EFFEXOR® Tablets:

Depressed patients who are currently being treated at a therapeutic dose with EFFEXOR® may be switched to EFFEXOR® XR at the nearest equivalent dose (mg/day), e.g., 37.5 mg EFFEXOR® two-times-a-day to 75 mg EFFEXOR® XR once daily. However, individual dosage adjustments may be necessary.

Patients With Hepatic Impairment:

Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared with normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by about 50% in patients with moderate hepatic impairment. For such patients, it may be desirable to start at 37.5 mg/day. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Patients with Renal Impairment

Given the decrease in clearance for venlafaxine and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR=10-70 mL/min) compared to normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be decreased by 25%-50%. In patients undergoing hemodialysis, it is recommended that patients, it may be desirable to start at 37.5 mg/day. Since there is so much individual variability in clearance among patients with renal impairment, individualization of dosing may be desirable.

Elderly Patients

No dose adjustment is recommended for elderly patients solely on the basis of their age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Maintenance/Continuation/Extended Treatment

There is no body of evidence available to answer the question of how long a patient should continue to be treated with venlafaxine. It is generally agreed that acute episodes of major depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Discontinuing Venlafaxine

When venlafaxine therapy that has been administered for more than 1 week is stopped, it is generally recommended that the dose be tapered gradually to minimize the risk of discontinuation symptoms. Patients who have received venlafaxine for 6 weeks or more should have their dose tapered gradually over a 2-week period. Individualization of tapering may be necessary.

Switching Patients to or from a Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with venlafaxine. In addition, at least 14 days should be allowed after stopping venlafaxine before starting an MAOI (see "Contraindications").

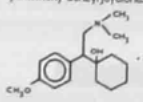
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Venlafaxine Hydrochloride

Chemical Name: (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride; or (±)-1-[α[(dimethylamino)methyl]-p-methoxy-benzyl]cyclohexanol hydrochloride

Structural Formula:



Molecular Weight: 313.87

Physical Form: White to off-white crystalline solid

Solubility:

Water:	540, 542, 501 and 21.6 mg/mL at pH 1.0, 5.38, 7.09 and 7.97
Ethanol:	91.7 mg/mL
Propylene Glycol:	200 mg/mL
Glycerin:	115 mg/mL
pKa value:	9.4

Composition:

EFFEXOR® Tablets

Medicinal Ingredients	Non-medicinal Ingredients:	
Venlafaxine Hydrochloride	Microcrystalline cellulose, NF	Ferric Oxide, NF Yellow
	Lactose, NF Hydrous	Sodium Starch Glycolate, NF
	Cosmetic Brown Iron Oxide	Magnesium Stearate, NF

Stability and Storage Recommendations

Store at room temperature (15-30°C), in a dry place.

EFFEXOR® XR Capsules (extended release)

Medicinal Ingredients	Non-medicinal Ingredients:	
Venlafaxine Hydrochloride	Ethylcellulose, NF	Titanium Dioxide, USP
	Gelatin, NF	White Tek SB-0007 and/or Opacode
	Hydroxypropylmethyl Cellulose, USP	Red S-1-19034 ink
	Iron Oxide, NF	Talc, USP
	Microcrystalline Cellulose, NF	

Stability and Storage Recommendations

Store at room temperature (15-30°C), in a dry place.

AVAILABILITY OF DOSAGE FORMS

"EFFEXOR® (venlafaxine HCl) Tablets are available, in bottles of 100 tablets, in the following tablet strengths *(potency is expressed in terms of venlafaxine base)*:

37.5 mg Shield-shaped, peach-coloured compressed tablet, with a score, with "**W**" on one side and "37.5" on the other side.

75 mg Shield-shaped, peach-coloured compressed tablet, with a score, with "**W**" on one side and "75" on the other.

"EFFEXOR® XR (venlafaxine HCl) Capsules are available in bottles of 100 capsules and 500 capsules, in the following dosage strengths *(potency is expressed in terms of venlafaxine base)*:

37.5 mg Hard gelatin capsule with grey cap and peach body, with "**W**" and "Effexor XR" on the cap and "37.5" on the body, in red ink.

75 mg Hard gelatin capsule with peach cap and body, with "**W**" and "Effexor XR" on the cap and "75" on the body, in red ink.

150 mg Hard gelatin capsule with dark orange cap and body, with "**W**" and "Effexor XR" on the cap and "150" on the body, in white ink.

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

REFERENCES:

1. Guidelines for Treatment of Depression and Anxiety Disorders, Canadian Network for Mood and Anxiety Treatment (C.A.N.M.A.T.), Toronto, 1998.
2. Thase M, Rush J, Kasper S, et al. Tricyclics and newer antidepressant medications: treatment options for treatment-resistant depressions. *Depression* 1995; 2:152-168.
3. Effexor®/ Effexor® XR Product Monograph, Wyeth-Ayerst Canada Inc.

Product Monograph available on request.

WYETH-AYERST CANADA INC.
Montreal, Canada
H4R 1J6

LOSEC®

(omeprazole magnesium)

TRUSTED ACID CONTROL

10 and 20 mg delayed release tablets

H^+, K^+-ATPase Inhibitor

NOTE: When used in combination with amoxicillin, clarithromycin or metronidazole, the Product Monographs for those agents must be consulted and followed.

ACTIONS AND CLINICAL PHARMACOLOGY

Omeprazole inhibits the gastric enzyme H^+,K^+-ATPase (the proton pump) which catalyzes the exchange of H^+ and K^+. Omeprazole is effective in the inhibition of both basal acid secretion and stimulated acid secretion. The inhibition is dose-dependent. Daily oral doses of omeprazole 20 mg and higher showed a consistent and effective acid control. Information from clinical trials in patients with duodenal ulcers in remission indicate that LOSEC (omeprazole magnesium) 20 mg tablets demonstrate the same inhibition of stimulated acid secretion and similar effect on 24-hour intragastric pH as LOSEC 20 mg capsules. The mean decrease in peak acid output after pentagastrin stimulation was approximately 70%, after 5 days of dosing with LOSEC 20 mg tablet once daily. The equivalence of two 10 mg LOSEC (omeprazole magnesium) tablets to one 20 mg LOSEC tablet (omeprazole magnesium) has been demonstrated by a bioequivalence study in healthy volunteers. Treatment with LOSEC alone has been shown to suppress, but not eradicate *Helicobacter pylori (H. pylori)*, a bacterium that is strongly associated with acid peptic disease. Approximately, 90 to 100% of patients with duodenal ulcers, and 80% of patients with gastric ulcer, are infected with *H. pylori*. Clinical evidence indicates a synergistic effect between omeprazole and certain antibiotics in achieving eradication of *H. pylori*. Eradication of *H. pylori* is associated with symptom relief, healing of mucosal lesions, decreased rate of duodenal ulcer recurrence and long-term remission of peptic ulcer disease, and reducing the need for prolonged anti-secretory therapy. There is no statistically significant change in the bioavailability (AUC, C_{max}) of amoxicillin during concomitant treatment with omeprazole, in healthy volunteers. There is an increase in the bioavailability (AUC) and half-life of omeprazole, and bioavailability (AUC) and C_{max} of clarithromycin, during concomitant administration, in healthy volunteers. There is no statistically significant change in the bioavailability (AUC, C_{max}) of metronidazole during concomitant treatment with omeprazole, in healthy volunteers. LOSEC tablets are absorbed rapidly. Food has no effect on the bioavailability of the tablet. Peak plasma levels occur on average within 2 hours. The 20 mg tablet and the 20 mg capsule are not bioequivalent in terms of plasma omeprazole AUC, C_{max} and t_{max}. LOSEC 20 mg tablets demonstrate, after repeated dosing, increased plasma omeprazole AUC (18%) and maximum concentration (41%) in comparison to omeprazole 20 mg given as capsules. The omeprazole capsule (as a multiple unit formulation) is usually emptied gradually from the stomach into the intestine. In contrast to the capsule, the tablet (as a single unit formulation) will enter the intestine and dissolve as one unit. Consequently, the absorption and first-pass metabolism of the tablet take place only during a very limited period. This may be one of the reasons for the difference observed in the pharmacokinetic variables of the two formulations. The antisecretory effect of omeprazole is directly proportional to the AUC; it is not dependent on the plasma concentration at any given time. Omeprazole is 95% bound to plasma proteins. Omeprazole undergoes first-pass metabolism by the cytochrome P-450 2C19 system, mainly in the liver. Following i.v. administration and oral administration (capsules) of omeprazole, 80% of the dose is recovered as urinary metabolites. The remaining 20% is excreted in the feces. LOSEC 20 mg tablets and LOSEC 20 mg capsules have an equivalent pharmacodynamic effect assessed by the inhibition of stimulated acid secretion and effect on 24-hour intragastric pH.

INDICATIONS AND CLINICAL USE

LOSEC (omeprazole magnesium) tablets are indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as 1. duodenal ulcer; 2. gastric ulcer; 3. NSAID-associated gastric and duodenal ulcers; 4. reflux esophagitis; 5. symptomatic gastroesophageal reflux disease (GERD), *i.e.*, heartburn and regurgitation; 6. Zollinger-Ellison syndrome (pathological hypersecretory condition); 7. eradication of *H. pylori*. LOSEC, in combination with clarithromycin and either amoxicillin or metronidazole, is indicated for the treatment of patients with peptic ulcer disease associated with *Helicobacter pylori* infection. The optimal timing for eradication therapy in patients whose ulcer is not clinically active (*i.e.*, asymptomatic) remains to be determined. Patients who fail to have their infection eradicated may be considered to have *H. pylori* resistant to the antimicrobials used in the eradication regimen. Therefore, therapy involving alternative effective antimicrobial agents should be considered (if re-treating). It has been demonstrated that resistance to metronidazole is a negative predictive factor, decreasing the eradication rate of *H. pylori* obtained with triple therapy (omeprazole, metronidazole and clarithromycin) by 10-20%. The addition of omeprazole to metronidazole and clarithromycin appears to reduce the effect of primary resistance and the development of secondary resistance compared to antimicrobials alone.

Table 1. Results of studies in patients with a history of duodenal ulcer who were *H. pylori*-positive.

	Treatment	Eradication Rate	
		APT or ITT Analysis	PP Analysis
Study 1	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	95%	98%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	95%	94%
Study 2	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	94%	95%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	87%	91%

*500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety.

Study 1: Patients included in the APT and PP analyses were assessed for *H. pylori* status by UBT pre- and post-treatment, n = 684 (APT analysis).

Study 2: Patients included in the ITT and PP analyses were assessed for *H. pylori* status by UBT and culture pre- and post-treatment, n = 514 (ITT analysis).

Table 2. Results of studies in patients with active peptic ulcer who were *H. pylori*-positive (ITT analysis).

	Treatment	Eradication Rate (PP analysis)	Ulcer Healing Rate (post-treatment)	Rate of Patients in Remission (6 months after cessation of therapy)
Study 3	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	78% (87%)	92%	88%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	85% (92%)	94%	92%
Study 4	omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg, all twice daily for one week	79% (83%)	94%	83%
	omeprazole 20 mg + metronidazole 400 mg* + clarithromycin 250 mg, all twice daily for one week	86% (93%)	96%	92%

*500 mg metronidazole appears to be equivalent to 400 mg with regards to efficacy and safety.

Study 3: Patients with duodenal ulcer, included in the ITT analysis, were assessed for *H. pylori* status by UBT and histology pre- and post-treatment, n = 146 (ITT analysis).

Study 4: Patients with gastric ulcer, included in the ITT analysis, were assessed for *H. pylori* status by UBT and histology pre- and post-treatment, n = 145 (ITT analysis).

CONTRAINDICATIONS Hypersensitivity to omeprazole or any of the components of this medication.

WARNINGS When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with LOSEC (omeprazole magnesium) tablets is instituted, as treatment with omeprazole may alleviate symptoms and delay diagnosis.

Use in Pregnancy The safety of omeprazole in pregnancy has not been established. LOSEC tablets should not be administered to pregnant women unless the expected benefits outweigh the potential risks. **Nursing Mothers** It is not known if omeprazole is secreted in human milk. LOSEC tablets should not be given to nursing mothers unless its use is considered essential. **Use in Children** The safety and effectiveness of LOSEC tablets in children have not yet been established.

PRECAUTIONS

Use in the Elderly Elderly subjects showed increased bioavailability (36%), reduced total plasma clearance (to 250 mL/min) and prolonged (50%) elimination half-life (to 1.0 hour) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). The daily dose in elderly patients should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION). **Patients with Hepatic Insufficiency** Patients with impaired liver function showed a 75% increase in bioavailability, reduced total plasma clearance (to 67 mL/min), and a four-fold prolongation of the elimination half-life (to 2.8 hours) (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules). A dose of 20 mg omeprazole capsules given once daily to these patients for 4 weeks was well tolerated, with no accumulation of omeprazole or its metabolites. The daily dose in patients with severe liver disease should, as a rule, not exceed 20 mg (see DOSAGE AND ADMINISTRATION). **Patients with Renal Insufficiency** The disposition of intact omeprazole is unchanged in patients with impaired renal function, and no dose adjustment is needed in these patients (data obtained from studies with i.v. administration of omeprazole and oral administration of omeprazole capsules) (see DOSAGE AND ADMINISTRATION). Information on the bioavailability of LOSEC 20 mg tablet in elderly patients, in patients with hepatic insufficiency, and in patients with renal insufficiency, as well as information on drug interactions are not currently available. **Carcinogenicity** The rat carcinogenicity study (24 months) revealed a gradual development from gastric ECL-cell hyperplasia to carcinoids at the end of their normal life-span during administration with 14-140 mg/kg/day of omeprazole. No metastasis developed. No carcinoids developed during 18 months' high-dose treatment of mice (14-140 mg/kg/day). Similarly, administration of omeprazole up to 28 mg/kg/day in dogs for 7 years did not cause any carcinoids. The gastric carcinoids in rats were related to sustained hypergastrinemia secondary to acid inhibition and not to omeprazole per se. Similar observations have been made after administration of histamine H_2-receptor blockers and also in partially fundectomized rats. Short-term treatment and long-term treatment with omeprazole capsules in a limited number of patients for up to 6 years have not resulted in any significant pathological changes in gastric oxyntic endocrine cells. **Drug Interactions** The absorption of some drugs might be altered due to the decreased intragastric acidity. Thus, it can be predicted that the absorption of ketoconazole will decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids. Omeprazole is metabolized by the cytochrome P-450 system (CYP), mainly in the liver. The pharmacokinetics of the following drugs, which are also metabolized through the cytochrome P-450 system, have been evaluated during concomitant use of omeprazole capsules in humans: aminopyrine, antipyrine, diazepam, phenytoin, warfarin, theophylline, propranolol, metoprolol, lidocaine, quinidine, ethanol, piroxicam, diclofenac and naproxen. Aminopyrine and Antipyrine: After 14 days' administration of 60 mg omeprazole once daily, the clearance of aminopyrine was reduced by 19%; the clearance of antipyrine was reduced by 14%. After 14 days' administration of 30 mg once daily, no significant changes in clearance were noted. **Diazepam, Warfarin and Phenytoin** As LOSEC is metabolized through cytochrome P-450 2C19, it can alter the metabolism and prolong elimination of diazepam, warfarin (R-warfarin) and phenytoin. Diazepam: Following repeated dosing with omeprazole 40 mg once daily, the clearance of diazepam was decreased by 54%. The corresponding decrease after omeprazole 20 mg was 26%. Warfarin: Concomitant administration of omeprazole 20 mg in healthy subjects had no effect on plasma concentrations of the (S)-enantiomer of warfarin, but caused a slight, though statistically significant increase (12%) in the less potent (R)-enantiomer concentrations. A small but statistically significant increase (11%) in the anticoagulant effect of warfarin was also seen. Concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin. Phenytoin: Following three weeks' treatment with omeprazole 20 mg once daily, the steady-state plasma levels of phenytoin in epileptic patients already receiving concomitant phenytoin treatment were not significantly affected. Urinary excretion of phenytoin and its main metabolite were also unchanged. After single intravenous and oral doses of omeprazole capsules 40 mg in young, healthy volunteers, the clearance of phenytoin was decreased by 15-20%, and half-life was prolonged by 20-30%. Following repeated dosing with omeprazole 40 mg once daily, the elimination half-life of phenytoin was increased by 27%. Thus, there appears to be a dose-dependent inhibition of elimination of phenytoin by omeprazole. Patients receiving phenytoin and warfarin should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with omeprazole. Results from a range of interaction studies with LOSEC versus other drugs indicate that omeprazole, 20-40 mg given repeatedly, has no influence on other clinically relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP 1A2 (caffeine, phenacetin, theophylline), CYP 2C9 (S-warfarin), CYP 2D6 (metoprolol, propranolol), CYP 2E1 (ethanol), and CYP 3A (cyclosporin, lidocaine, quinidine, estradiol). Theophylline: No effects on oral or i.v. theophylline kinetics have been observed after repeated once-daily doses of 40 mg omeprazole. Propranolol and Metoprolol: No effects on propranolol kinetics were observed in a steady-state trial with 20 mg of omeprazole daily. Similarly, no effects on steady-state plasma levels of metoprolol were observed after concomitant treatment with 40 mg omeprazole daily. Lidocaine: No interaction with a single intravenous dose of lidocaine or its active metabolite, MEGX, was found after one week's pre-treatment with omeprazole 40 mg once daily. There were no interactions between omeprazole and lidocaine or MEGX concerning pharmacokinetic variables. Quinidine: After one week of omeprazole 40 mg once daily, no effect was observed on the kinetics or pharmacodynamics of quinidine. Ethanol: There was no significant effect on the pharmacokinetics of ethanol after omeprazole 20 mg. Piroxicam, Diclofenac and Naproxen: There was no significant effect on the steady-state pharmacokinetics of piroxicam, diclofenac, and naproxen following repeated dosing with omeprazole 20 mg, in healthy volunteers. No interaction with food after repeated dosing of LOSEC tablets has been found. No interaction with antacids administered concomitantly with omeprazole (given as capsules) has been found.

ADVERSE REACTIONS Omeprazole is well tolerated. Most adverse reactions have been mild and transient, and have shown no consistent relationship with treatment. Adverse events have been recorded during controlled clinical investigations in 2764 patients exposed to omeprazole (data taken from controlled clinical studies with omeprazole capsules) or reported from routine use. In a controlled clinical trial comparing omeprazole to placebo, the prevalence of adverse events with omeprazole 40 mg once daily was similar to that with placebo. In short-term comparative double-blind studies with histamine H_2-receptor antagonists, there was no significant difference in the prevalence of adverse events between omeprazole capsules and the H_2-receptor antagonists. An extensive evaluation of laboratory variables has not revealed any significant changes during omeprazole treatment which are considered to be clinically important. The following adverse events (at a rate of more than 1%) have been reported in individuals receiving omeprazole capsules in controlled clinical situations: diarrhea (2.8%); headache (2.6%); flatulence (2.3%); abdominal pain (1.7%); constipation (1.3%); and dizziness/vertigo (1.1%). In addition, the following adverse events were reported in clinical trials or were reported from routine use: Skin: Rarely, rash and/or pruritus. In isolated cases photosensitivity, erythema multiforme and alopecia. Musculoskeletal: In isolated cases arthralgia, muscular weakness and myalgia. Central and Peripheral Nervous System: Rarely dizziness, paresthesia, somnolence, insomnia and vertigo. In isolated cases reversible mental confusion, agitation, depression and hallucination occurring predominantly in severely ill patients. Gastrointestinal: Nausea and vomiting. In isolated cases dry mouth, stomatitis and gastrointestinal candidiasis. Hepatic: In rare cases, increased liver enzyme levels. In isolated cases encephalopathy in patients with pre-existing severe liver disease, hepatitis with or without jaundice and hepatic failure. Endocrine: In isolated cases gynecomastia. Hematologic: In isolated cases, patients have developed leukopenia and thrombocytopenia, agranulocytosis and pancytopenia. Other: Rarely, malaise. Hypersensitive reactions including urticaria (rarely) and, in isolated cases, angioedema, fever, bronchospasm and interstitial nephritis and anaphylactic shock. In isolated cases increased sweating, peripheral edema, blurred vision and taste disturbances. *H. pylori* Eradication Combination Therapy: The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 493 patients receiving omeprazole, amoxicillin and clarithromycin: diarrhea (28%), taste disturbances (15%), headache (5%), flatulence (4%), nausea (3%), abdominal pain (2%), ALAT increased (1%), epigastric pain (1%), pharyngitis (1%) and glossitis (1%). The following adverse events (at a rate of more than 1%) were recorded during controlled clinical trials in 494 patients receiving omeprazole, metronidazole and clarithromycin: taste disturbances (14%), diarrhea (13%), headache (6%), ALAT increased (6%), flatulence (5%), nausea (5%), ASAT increased (5%), dyspepsia (3%), dry mouth (2%), dizziness/vertigo (2%), epigastric pain (1%), pharyngitis (1%), eructation (1%) and fatigue (1%). Clinical experience with the use of LOSEC 20 mg tablet is limited. In two short-term studies (20 mg tablet once daily for a maximum duration of 7 days) in a limited number of patients with duodenal ulcer in remission, the adverse event profile seen with the LOSEC 20 mg tablet is similar to that seen with the LOSEC 20 mg capsule.

SYMPTOMS AND TREATMENT OF OVERDOSAGE No information is available on the effects of higher doses in man, and specific recommendations for treatment cannot be given. Single oral doses of up to 400 mg of omeprazole capsules have not resulted in any severe symptoms, and no specific treatment has been needed. As in all cases where overdosing is suspected, treatment should be supportive and symptomatic. Any unabsorbed material should be removed from the gastrointestinal tract, and the patient should be carefully monitored. The oral LD_{50} of omeprazole in male and female rats and mice was greater than 4000 mg/kg. In dogs, the only sign

of acute toxicity was vomiting, which occurred at doses of approximately 600 mg/kg. When used in combination with antibiotics, the Prescribing Information/Product Monograph for those antibiotics should be consulted.

DOSAGE AND ADMINISTRATION LOSEC (omeprazole magnesium) 20 mg tablets and LOSEC 20 mg capsules have an equivalent effect on the inhibition of stimulated acid secretion and on 24-hour intragastric pH. These data support the conclusion that LOSEC 20 mg tablet and capsule can be used with equivalent efficacy in the treatment of conditions where a reduction of gastric acid secretion is required. **Duodenal Ulcer** Acute Therapy: The recommended adult oral dose is 20 mg given once daily. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional 2 weeks of treatment is recommended. Refractory Patients: In patients with duodenal ulcer refractory to other treatment regimens, the recommended adult doses are 20 mg and 40 mg given once daily. Healing is usually achieved within 4 weeks in such patients. Maintenance Therapy for Duodenal Ulcer: Over 95% of duodenal ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy, as described below. A small percentage of patients who are *H. pylori*-negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. The recommended LOSEC dose is 10 mg once daily, increased to 20-40 mg once daily as necessary. **Gastric Ulcer** Acute Therapy: The recommended adult dose is 20 mg given once daily. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended. Refractory Patients: In patients with gastric ulcer refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 weeks. Maintenance Therapy for Gastric Ulcer: About 80% of gastric ulcer patients are *H. pylori*-positive, and should be treated with eradication therapy, as described below. A small percentage of patients who are *H. pylori*-negative will experience a disease recurrence and will require maintenance treatment with an antisecretory agent. The recommended LOSEC dose is 20 mg once daily, increased to 40 mg once daily as necessary. **NSAID-Associated Gastric or Duodenal Ulcers** The issue of whether or not eradication of *H. pylori* in patients with NSAID-associated ulcers might have beneficial preventive effects has not yet been settled. Acute Therapy: In patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily. Symptom resolution is rapid and healing usually occurs within 4 weeks. For those patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended. Maintenance Therapy: For the prevention of relapse in patients with NSAID-associated gastric or duodenal ulcers, the recommended adult dose is 20 mg given once daily, for up to 6 months. ***Helicobacter pylori* Associated Peptic Ulcer Disease** Omeprazole, Amoxicillin and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is LOSEC 20 mg, amoxicillin 1000 mg and clarithromycin 500 mg, all twice daily for seven days. This dosing regimen can be known as LOSEC 1-2-3 A™. Omeprazole, Metronidazole and Clarithromycin Triple Therapy: The recommended dose for eradication of *H. pylori* is LOSEC 20 mg, metronidazole 500 mg and clarithromycin 250 mg, all twice daily for seven days. This dosing regimen can be known as LOSEC 1-2-3 M™. To ensure healing and/or symptom control, further treatment with 20 mg LOSEC once daily for up to three weeks is recommended for patients with active duodenal ulcer, and with 20-40 mg LOSEC once daily for up to twelve weeks for patients with active gastric ulcer. Patient compliance with treatment regimens for the eradication of *H. pylori* has been demonstrated to have a positive effect on eradication outcome. In clinical trials, patients treated with triple therapy regimens have shown high compliance rates. Susceptibility testing (MIC values derived from the Agar dilution method) of *H. pylori* to metronidazole and clarithromycin is available for 486 primary isolates from patients with a history of duodenal ulcer in one European study. Resistance to metronidazole (MIC >8 mg/L) was detected in 131 strains (27%), while9 strains (2%) were resistant to clarithromycin (MIC >1 mg/L). Secondary resistance to metronidazole developed in strains from 4 patients treated with omeprazole/metronidazole/clarithromycin. Similarly, in those patients treated with omeprazole/metronidazole/clarithromycin or omeprazole/amoxicillin/clarithromycin combinations, secondary resistance to clarithromycin developed in strains from 4 patients. For amoxicillin, the MIC values at pre-therapy or post-therapy did not indicate any primary, or the development of secondary, resistance to *H. pylori*. **Reflux Esophagitis** Acute Therapy: The recommended adult dose is 20 mg given once daily. In most patients, healing occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended. Refractory Patients: For patients with reflux esophagitis refractory to other treatment regimens, the recommended adult dose is 40 mg given once daily. Healing is usually achieved within 8 weeks. Maintenance Therapy for Reflux Esophagitis: For the long-term management of patients with healed reflux esophagitis, 10 mg omeprazole (given as capsules) once daily has been found to be effective in controlled clinical trials of 12 months' duration, and in continuous maintenance treatment, in a limited number of patients, for a period of up to 6 years. Therefore, the recommended adult dose of LOSEC tablets for maintenance treatment of patients with healed reflux esophagitis is 10 mg given once daily. In the case of recurrence, the dose can be increased to 20-40 mg once daily. **Symptomatic Gastroesophageal Reflux Disease (*i.e.*, Heartburn and Regurgitation)** The recommended adult dose is 20 mg given once daily. Symptom relief should be rapid. If symptom control is not achieved after 4 weeks, further investigation is recommended. Since some patients respond adequately to 10 mg given once daily, individual dose adjustment should be considered. For the maintenance of symptom relief in patients with gastroesophageal reflux disease (*i.e.*, heartburn and regurgitation) the recommended adult dose is 10 mg given once daily. **Zollinger-Ellison Syndrome** The dose used in the treatment of Zollinger-Ellison syndrome will vary with the individual patient. The recommended initial dose is 60 mg, given once daily. More than 90% of patients with the severe form of the disease and inadequate response to other therapies have been adequately controlled with doses of 20-120 mg omeprazole capsules daily. With doses greater than 80 mg, the dose should be divided and given twice daily. Doses should be adjusted to the individual patient's need and should continue as long as clinically indicated. Doses up to 120 mg omeprazole capsules three times daily have been administered. Patients with Renal Insufficiency: No dose adjustment is required **(see PRECAUTIONS)**. Patients with Hepatic Insufficiency: No dose adjustment is required. The daily dose should not exceed 20 mg **(see PRECAUTIONS)**. Elderly Patients: No dose adjustment is required. The daily dose should not exceed 20 mg **(see PRECAUTIONS)**. The tablets should be swallowed whole with sufficient water.

AVAILABILITY OF DOSAGE FORMS

LOSEC (omeprazole magnesium) 10 mg tablets are pink, circular and biconvex, printed LOSEC on both sides.
10

LOSEC (omeprazole magnesium) 20 mg tablets are red-brown, circular and biconvex, printed LOSEC on both sides.
20

The 10 mg tablets are provided in press-through blister compliance strips in cartons of 28. The 20 mg tablets are provided in press-through blister compliance strips in cartons of 14 and 28 and in 10 x 10 unit dose blister packages.

Full Product Monograph available on request.

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Manuscripts should be printed on standard 22x28 cm (letter-sized) paper. Submissions should be 3000 words (approximately 15 pages double spaced) or less. This word limit does not include references or figures. Longer submissions may be considered with prior permission from the Associate Editor-Reviews and the Editor-in-Chief. Pages should be numbered consecutively.

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Abstract: The abstract should appear on the second page and should be no longer than 250 words. It should state the purpose of the paper, basic procedures, main findings and the principal conclusions.

Text, Acknowledgements: These should conform to the *Uniform requirements for manuscripts submitted to biomedical journals* (CMAJ 1994:150:147-154). These are on reserve in Dalhousie University's Kellogg Library under reserve call #971.

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Journal article

1. Johansson E, Aspirisi T. Missing cruciate ligament in congenital short femur. *J Bone Joint Surg* 1983;65A(8):1109-1115.

Chapter in book

2. Hahn JF, Mason L. Low back pain in children. In: Hardy Rw Jr, ed. *Lumbar disc disease*. New York: Raven Press, 1982:217-28. (Seminars in neurological surgery).

Book

3. Katz J. *Common orthopedic problems in pediatric practice*. New York: Raven Press, 1981:125-7.

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