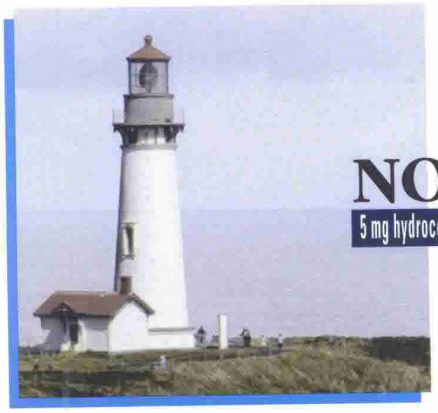
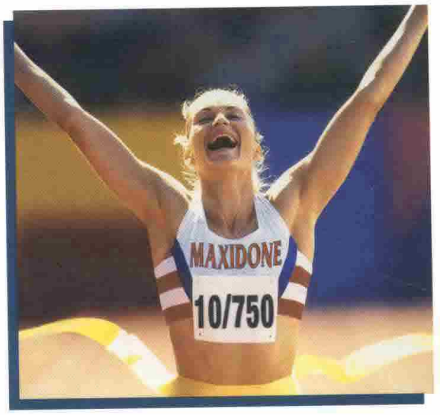


NORCO® 5/325 C III
5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

NORCO® 7.5/325 C III
7.5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP



TRAINING BINDER

MAXIDONE™ C III
hydrocodone bitartrate and acetaminophen tablets, USP 10 mg/750 mg

WATSON Pharma, Inc.
A Subsidiary of Watson Laboratories, Inc.

Training material only. Not for use in promotion.

PLAINTIFF TRIAL EXHIBIT
P-28864_00001

Introduction

Norco® and **Maxidone™** are oral, combination, narcotic analgesics that offer four unique formulations of hydrocodone bitartrate and acetaminophen: **Norco® 5/325** (5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP), **Norco® 7.5/325** (7.5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP), **Norco® 10/325** (10 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP), and **Maxidone™** (10 mg hydrocodone bitartrate and 750 mg acetaminophen tablets, USP). All four formulations are Schedule III narcotics indicated for the treatment of moderate to moderately severe pain. What sets **Norco®** apart from other hydrocodone/acetaminophen combinations is a low, 325-mg dose of acetaminophen that may be less than half of that provided by competing products. This is an important difference, as providing enough hydrocodone to treat pain without exceeding the 4-gram maximum daily dose of acetaminophen has become a very real concern for many prescribing physicians. As you will learn in this manual, acetaminophen is not as benign a drug as has been previously believed, so there are definite advantages to this lower dose of acetaminophen in some patient populations.

Maxidone™ offers the highest strength hydrocodone (10 mg) and acetaminophen (750 mg), offering physicians the most potent combination of these two compounds. For our purposes, this manual will concentrate on the products offering the most potential in the analgesic market, **Norco® 5/325, Norco® 7.5/325,** and **Maxidone™**.

The usual adult dosage of **Norco® 5/325** is one or two tablets every 4 to 6 hours, as needed for pain. With this strength, physicians have the opportunity to titrate up to 2 tablets q4–6h if the patient's pain is not controlled, or down to 1 tablet q4–6h if the patient is well controlled or experiencing side effects.

The usual adult dosage of **Norco® 7.5/325** is one tablet every 4 to 6 hours, as needed for pain. This gives physicians considerably more flexibility when prescribing this popular hydrocodone dose, as there is less chance of exceeding the 4-gram daily acetaminophen limit than with the use of a combination such as Lortab 7.5/500, Vicodin ES (7.5/750), or Lorcet 7.5/650.

Norco® 10/325 has a dosage schedule of one tablet every 4 to 6 hours, with a maximum of six tablets per day. **Norco® 10/325** provides the highest recommended daily dosage of hydrocodone but at just half the daily recommended maximum dosage of acetaminophen.

The usual adult dosage of **Maxidone™** is one tablet every 4 to 6 hours, as needed for pain up to a maximum of 5 tablets per day. **Maxidone™** is an excellent choice in otherwise healthy patients, those without hepatic or renal impairment, hypothyroidism, prostatic hypertrophy, Addison's disease, or urethral stricture.

The materials in this binder have been compiled to capitalize on the advantages of these formulations. In them you'll have the ammunition to successfully promote **Norco® 5/325**, **Norco® 7.5/325**, and **Maxidone™**. Sections within this training manual discuss the pathophysiology of pain and basic mechanisms of pain control, along with full discussions of the category, marketplace, and competition. Furthermore, the more important competitive brands are detailed separately, and specific arguments are provided for each of these brands.

As was the case with **Norco® 10/325**, sales of these products will be driven through the field force, and we will support your efforts to the fullest degree possible.

Welcome aboard.

Table of Contents

The Pathophysiology of Pain

Why Pain?

Pain is a protective mechanism, a signal that a part of the body is being damaged. Depending on its severity, pain will force the affected person to take action to stop the cause of the pain. Even a simple activity like sitting for a long time in one position can cause tissue damage by blocking blood flow to different areas of the skin. This interruption of the blood flow—called *ischemia*—will eventually cause these areas of skin to hurt, and the person will unconsciously shift his or her weight before any damage is done. A person who has lost this sense of pain will not be aware of the signal, and must therefore learn to automatically shift position every so often to avoid damaging skin or muscles. Such is the case in patients with debilitating injuries or diseases that result in both sensory and motor damage, such as spinal cord injury or diabetes.

Pain is one of the most common problems afflicting humans, and is the most common symptom for which patients seek medical evaluation. In the United States alone, an estimated 34 million adults suffer from mild to moderate nonmalignant pain. In addition, patients report that pain is the most distressing symptom of illness or trauma. This is unfortunate, because the potent analgesics currently available are both safe and effective when properly selected and used. In fact, the greatest abuse with narcotic analgesics is not inducing addiction but rather the fear of inducing addiction; the result is the use of too little medication too infrequently to control pain.

Two Types of Pain

Pain has been classified into two categories: *acute pain* and *chronic pain*. Acute pain is defined as a state in which an individual experiences the presence of severe discomfort or an uncomfortable sensation. Examples include a toothache, a bone break, or a headache. Acute pain has a sudden onset and usually subsides with treatment. Acute pain is often described as sharp, pricking, fast, and electric.

Table 1.1 Characteristics of Acute and Chronic Pain

Acute Pain	*Chronic Pain*
• Sudden onset	• Lasts more than 3 months
• "Sharp"	• "Aching" or "throbbing"
• Defined area of pain	• Affected area is large or inconstant
• Responds quickly to treatment	• Does not respond to treatment immediately, or affects nervous system

Think of the shocking "zing" you feel when your dentist hits a nerve with his drill—that is acute pain.

Chronic pain is defined as a state in which an individual experiences pain that continues for 3 to 6 months or longer. Examples include the often difficult-to-treat pain associated with *malignancies* and rheumatoid arthritis. Such pain is described as throbbing, aching, and nauseating; it is usually associated with tissue destruction.

Patients with acute pain usually give a clear description of the pain's location, character, and timing, leading to an *etiologic* diagnosis. For instance, a man who comes into a doctor's office with a suspected broken left arm can typically tell the physician that the pain is centralized in his left arm—not his right arm—is sharp in character, and began when the man fell from a tree. Other objective signs and *autonomic* nervous system activity are also present in acute pain and include *diaphoresis* (severe perspiration), *tachycardia*, and *hypertension.*

Pain Receptors

Pain receptors are transmitters that notify the brain of possible tissue damage. The pain receptors in the skin and other tissues are all free nerve endings, ready for any external or internal assault. The receptors are widespread in the superficial layers of the skin and also in certain internal tissues, such as the *periosteum*—the thick fibrous membrane that covers the bones—as well as the arterial walls, the joint surfaces, and the *neurocranium*—the bones of the skull that enclose the brain.

Table 1.2 Pain Stimuli

- Physical stress to joint or muscle
- Blockage of blood flow
- Tissue damage
- Heat and cold
- Muscle spasm
- Damage to pain receptors
- Chemicals, eg, histamine, prostaglandins

Most of the other deep tissues are not extensively supplied with pain endings, but are rather weakly supplied. Nevertheless, any widespread tissue damage can still add up to cause pain in these areas.

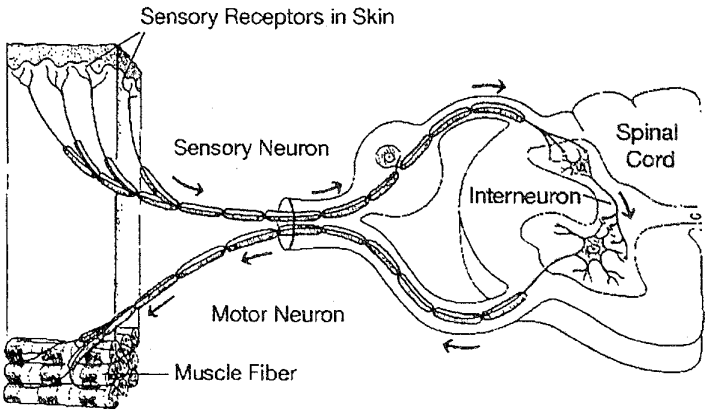
Pain receptors can be activated through mechanical, thermal, or chemical stimuli. Some pain receptors are excited almost entirely by one type of stimulus—excessive mechanical stress or tissue damage, extremes of heat or cold, and chemical substances such as *bradykinin*, *serotonin*, *histamine*, acids, *prostaglandins,* and *proteolytic* enzymes—but most pain receptors are sensitive to more than one type of stimulation.

Unlike most other sensory receptors of the body, such as the tactile receptors, pain receptors are not very adaptable to continuous stimulation. For example, tactile

receptors filter out the continuous stimulation caused by wearing clothing. Can you imagine how uncomfortable it would be to constantly feel the clothes covering your body? The newest fashions would leave very little to the imagination! However, pain sensors never show this type of adaptability; in fact, under some conditions, the threshold for excitation of the pain fibers becomes progressively lower and lower as the pain stimulus continues, thus allowing the receptors to become increasingly more activated with time. This increase in sensitivity of the pain receptors is called *hyperalgesia*.

Pain receptors fail to adapt to a constant stimulus for one reason: pain keeps the person aware of a damaging stimulus for as long as the stimulus persists.

Figure 1.1



Once stimulated, pain receptors send a signal along the neuron to the spinal cord. The spinal cord sends a message back to stimulate motor function, such as a retreat from the source of the pain, or relays the pain message to the brain. (Adapted from: Curtis H. *Biology.* New York, NY: Worth Publishers, Inc.; 1979:637.)

Transmitting Pain Signals to the Brain

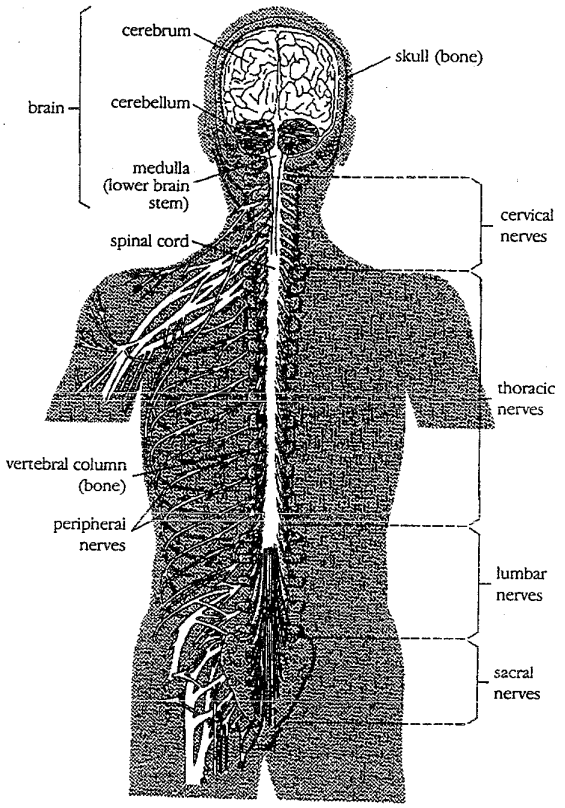
Even though all pain endings are free nerve endings, these endings use two separate pathways to transmit pain signals to the *central nervous system (CNS)*. The two pathways correspond to the two different types of pain: an acute or "fast" pain pathway and a chronic or "slow" pain pathway.

The fast pain signals are transmitted in the peripheral nerves to the spinal cord by "acute" pain fibers at velocities from 6 to 30 meters per second. Slow pain signals travel along the "slow" pain fibers at 0.5 to 2 meters per second.

Because of this double system of pain perception, a sudden painful event causes a dual pain sensation: a fast, sharp pain followed a second or so later by a slow, burning pain. A good example is the pain that you feel after hitting your thumb with a hammer: the initial, sharp pain comes first, followed by the throbbing slow pain that can last for hours or even days afterward.

The sharp pain apprises you very rapidly of the damaging influence of the hammer and, therefore, plays a role in making you react immediately to move your thumb away from the cause of the pain. On the other hand, the throbbing, slow pain tends to become more and more painful over time, and reinforces a reluctance to repeat the event. So acute pain comprises both fast and slow pain sensations.

Figure 1.2

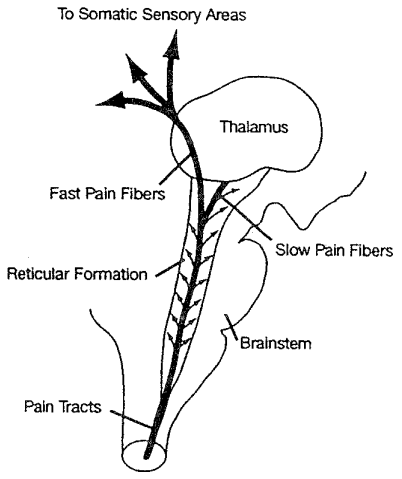


A diagram of the central nervous system, pictured from the back. The branching of the peripheral nerves from the spinal cord can be seen. (Adapted from: Luciano DS, Vander RJ, Sherman JH. *Human Structure and Function.* New York: McGraw-Hill; 1978:244.)

Both pain pathways enter the brain stem from the spinal cord, but do so in different ways. The acute fast pain pathway terminates in the *somatic* sensory areas of the brain, and goes through the *thalamus*, a part of the brain that serves as a relay station for the senses. This pathway locates the pain—within one-half inch from the stimulated area—so that the pain stimulus can be removed from the area, or vice versa.

In contrast to the fibers of the fast pain pathway, those of the slow pathway terminate almost entirely in the *reticular* formation of the brain stem, the part of the brain that controls eye movement, cardiovascular function, and *equilibrium*. However, great numbers of signals are relayed upward from the spinal cord through this area of the brain stem to other parts of

Figure 1.3 Pain Pathways



The fast pain signals are transmitted in the peripheral nerves to the spinal cord at speeds of up to 30 meters per second, while slow pain signals travel no faster than 2 meters per second.

the brain. Thus, the slow pain fibers have a very potent effect in activating essentially the entire nervous system, and have the potential to arouse one from sleep, create a sense of excitement or urgency, and promote the defense and aversion reactions designed to rid the person of the painful stimulus.

The signals that are transmitted through the slow pathway can be localized only to very general areas of the body. These signals are designed almost entirely for the single purpose of calling an individual's attention to injurious processes in the body, and can create sensations ranging from mild discomfort to intolerable suffering.

Section 1 Summary

- There are two types of pain: acute and chronic. Acute pain has a sudden onset (eg, after an injury), is described as sharp, occurs in a defined area, and responds quickly to treatment. Chronic pain usually lasts more than 3 months, is described as aching or throbbing, may occur over a large undefined area, and does not respond immediately to treatment.
- Pain receptors notify the brain of possible tissue damage. Unlike other receptors in the body, pain receptors do not adapt to continuous stimulation; they remain activated as long as the painful stimulus persists.
- There are two pain pathways that enter the brain stem from the spinal cord: a "fast" pain pathway and a "slow" pathway. The signals of the fast pain pathway locate the pain precisely so that the pain stimulus can be removed from the painful area. The signals of the slow pain pathway activate the entire central nervous system to call attention to the injurious processes in the body. These signals can result in sensations ranging from mild discomfort to intolerable suffering.

Mechanisms of Pain Control

The Central Analgesia System

The brain and spinal cord have the ability to control the number of pain signals they receive by activating a natural pain control system, called the *analgesia* system. This system is capable of blocking both the fast and slow pathways described in Section 1.

The analgesia system inhibits incoming pain signals at the level of the spinal cord by sending opposing signals that originate in the areas of the brain known as the *mesencephalon* and upper *pons*. These signals cause chemical transmitters to be released at various points along the spinal cord, blocking incoming pain signals before they are relayed to the brain.

The brain also has its own opiate system, secreting substances called *endorphins* that are similar to morphine. Receptors for these naturally occurring *analgesics* have been found at different points in the brain and the spinal cord, and a number of endorphins have been found throughout the central nervous system (see Table 2.1).

Table 2.1 The Opiate Receptors

Class	*Location*	*Function*
Mu-1	Brain	Relieve pain
Mu-2	Spinal cord	Slow respiration, inhibit gastrointestinal function, provide sedation, slow heartbeat
Kappa	Brain, spinal cord	Relieve pain, provide sedation, contract the pupil
Sigma	Brain	Relieve pain, create feeling of euphoria, stimulate respiration, dilate blood vessels

Endorphins bind to the same receptors that bind external opiates like morphine and, for that reason, are of interest to researchers trying to develop more potent pain-control medications. A listing of the proposed functions and locations of endorphins can be found in Table 2.2.

Although many of the details of the brain's analgesia system are not completely understood, it is known that the activation of this system, either by nervous signals entering the upper pons and mesencephalon or by the release of endorphins, can totally suppress many pain signals entering through the peripheral nerves.

Table 2.2 Endorphin Classes

Group	Location	Function
Pro-opiomelanocortin (POMC)	Brain, spinal cord, pituitary gland	Stimulate pain relief, stimulate adrenal glands
Pro-enkephalin	Adrenal glands, brain, spinal cord, pituitary gland, stomach, intestines	Transmit pain perception, regulate emotions
Pro-dynorphin	Adrenal glands, brain, spinal cord, pituitary gland, stomach, intestines	Ease pain

Prostaglandins: Messengers of Pain

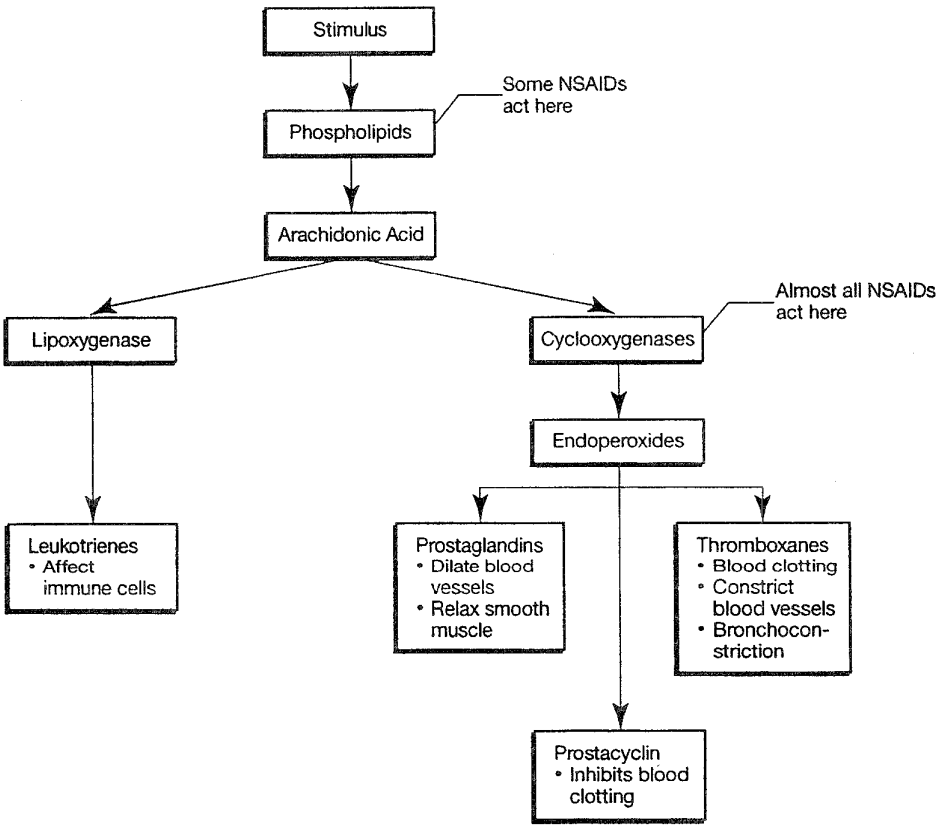
Prostaglandins are substances found throughout the body that have the ability to cause a variety of localized changes in many tissues, including vasodilation, vasoconstriction, and muscle stimulation. Whereas part of our perception of pain takes place in the brain, via the direct stimulus of peripheral nerves that send signals through the spinal cord to the brain, prostaglandins operate directly at the site of the pain. These substances play a major role in the inflammation process.

Prostaglandins act when an arthritic joint is red, hot, and swollen, a bone is broken, or a tooth has been extracted. They trigger local nerve endings that send a pain message to the brain. The prostaglandins do not cause overt pain, rather they sensitize nerve endings to the actions of histamine and *bradykinin*, natural chemicals that activate the fast and slow pain pathways.

Inflammation

Inflammation is the response of living tissues to injury. Inflammation occurs when a cell membrane is damaged or disturbed in any way—by heat or cold, by foreign substances such as organisms, drugs or chemicals, or by trauma. In response to the damage, *phospholipids* in the cell membrane stimulate the production of *arachidonic acid*, a precursor of the prostaglandins. Arachidonic acid is also a building block of *leukotrienes*, the substances that play a role in allergic responses, vasoconstriction, and increased vascular permeability (see Figure 2.1).

Figure 2.1 The Inflammation Cascade



Many of the drugs we use to stop inflammation interfere with the synthesis of the prostaglandins. How does this occur? Remember that arachidonic acid production is stimulated when tissues are damaged. This acid is then converted into leukotriencs by way of the enzyme 5-lipoxygenase, and into prostaglandin by way of the enzyme *cyclooxygenase* (COX). The COX enzyme is the basis for analgesic pharmacology.

Two forms of COX are now thought to exist: COX-1 and COX-2. COX-1 can be considered to be the housekeeping enzyme because it synthesizes prostaglandins that regulate normal cell activity. For example, prostaglandin E-2 protects the stomach mucosa from damage by irritating foods, excess stomach acid, and ulcer-causing drugs like indomethacin.

COX-2, in contrast, is activated by tissue damage. Little or no COX-2 is found in resting cells. However, inflammatory stimuli induce the synthesis of COX-2 in migratory cells, such as *macrophages*—cells involved in the immune response—that results in the release of prostaglandins. The release of prostaglandins with other inflammatory mediators, such as reactive oxygen radicals, results in inflammation.

The activity of drugs that decrease inflammation is centered on the interruption of the production of prostaglandin inflammatory mediators. Corticosteroids, such as dexamethasone (Decadron), interfere with the production of arachidonic acid. When arachidonic acid is stopped from being produced, both leukotriene and prostaglandin production is inhibited. *NSAIDs* (nonsteroidal anti-inflammatory drugs) interfere with the production of COX enzymes.

New insights into the mode of action of NSAIDs show that some of these agents are more prone to inhibiting COX-2 than COX-1. Piroxicam (Feldene), for instance, is 250 times more active on COX-1 than COX-2; aspirin is 166 times more active and indomethacin is 60 times more active. Because the drugs are more likely to shut off the supply of COX-1, the housekeeping enzyme, the supply of prostaglandin E-2 is diminished; it is no coincidence, then, that these particular drugs are also well known for their propensity to cause gastric bleeding. Compounds that affect both COX enzymes more equally should have less side effects and cause less irritation to the stomach. Acetaminophen is only 7 times more active on COX-1 than COX-2, but its antiinflammatory activity is also low. Flurbiprofen (Ansaid), which is slightly more active against COX-1, and diclofenac (Cataflam, Voltaren) and naproxen (Naprosyn, Anaprox, Naprelan), which have slightly greater activity against COX-2, all have minimal damaging effects on the GI tract. The target for new medicines is therefore focused on anti-inflammatory agents that are more COX-2 specific, to handle the inflammation response without causing the anti-COX-1 (gastric) side effects.

Section 2 Summary

- The CNS can activate its own analgesia system by secreting endorphins, naturally occurring morphine-like substances that can suppress the pain signals that enter through the peripheral nerves.
- Prostaglandins send messages of pain to the brain by sensitizing nerve endings to the actions of histamine and bradykinin, natural chemicals that activate the fast and slow pain pathways.
- Many analgesics act by inhibiting prostaglandin synthesis or blocking the relay of pain messages to the brain.
- Cyclooxygenase (COX) is a key enzyme in the synthesis of prostaglandins. It exists in two isoforms: COX-1 and COX-2. COX-1 is responsible for the synthesis of prostaglandins that protect the stomach mucosa from damage by excess stomach acid, irritating foods, and ulcerogenic drugs. COX-2 is responsible for the release of prostaglandins that are involved in the inflammation process.
- Some drugs are much more likely to inhibit COX-1 than COX-2, including the traditional NSAIDs and aspirin, and are thus associated with GI adverse effects. Others are more specific for COX-2, such as diclofenac, naproxen, and the COX-2 inhibitors (eg, celecoxib [Celebrex], rofecoxib [Vioxx], etc.) and thus have less associated GI adverse effects.

Effective Pain Management

Managing Pain

Pain can be controlled by pharmacological agents in two ways. First, pain can be stopped by blocking prostaglandin production at the injured site. The other way to control pain is by blocking the perception of pain in the brain.

Non-narcotic Analgesics

The *NSAIDs* include the salicylates (eg, *aspirin*), propionates (eg, ibuprofen), acetates (eg, indomethacin [Indocin]), fenamates (eg, meclofenamate [Meclomen]), and oxicams (eg, piroxicam [Feldene]). NSAIDs primarily inhibit the synthesis and release of prostaglandins *peripherally*, at the site of injury, by interfering with COX production. This effect in inflamed tissue is believed to be responsible for their analgesic and anti-inflammatory activity. Salicylates, such as aspirin, also block the generation of pain impulses and may also have a central analgesic action in the *hypothalamus*—the part of the brain that regulates signals passing back and forth from the spinal cord.

COX-2 inhibitors represent a refinement to standard NSAIDs, which act against both COX-1 and COX-2 enzymes—and in many cases, more strongly against COX-1. As their name implies, COX-2 inhibitors were designed to preferentially block COX-2. As described on page 2.4, the COX-2 enzyme, activated by tissue damage, triggers the inflammatory process by contributing to the synthesis of prostaglandins. Three such products were on the market as of this update: celecoxib (Celebrex), rofecoxib (Vioxx), and meloxicam (Mobic).

The benefit of COX-2 inhibitors was supposed to be an absence of the gastrointestinal symptoms commonly observed with standard NSAIDs. Recent studies, however, have reported gastrointestinal side effects in at least a portion of these patients, suggesting that they do indeed block COX-1. The GI symptoms remain much less common than they are with standard NSAIDs, and particularly severe symptoms, such as ulcers, occur rarely, but all of these gastric effects occur more commonly with COX-2 inhibitors than they do with acetaminophen.

COX-2 inhibitors are contraindicated in patients with hepatic or renal insufficiency, asthma, or allergies to NSAIDs or sulfonamides. They also increase bleeding time in patients who take warfarin.

Acetaminophen appears to produce its analgesic effect by inhibiting prostaglandin synthesis primarily in the CNS. Although inhibition of prostaglandins also occurs at peripheral sites, such activity occurs at a much lower level than with the NSAIDs, and the anti-inflammatory effects of acetaminophen are minimal. The analgesic effect

of acetaminophen is comparable to that of aspirin. The exact mechanisms of action of acetaminophen are unknown.

Opiates

Opium in its crude form was used well into the 19th century before its chief alkaloid, *morphine*, was isolated. Morphine is considered to be the prototype of the *agonist* drugs, that is, drugs capable of combining with receptors to initiate a drug action. The discovery of other *alkaloids* soon followed and their use came to be preferred to that of the crude opium preparations. *Opiate* refers to drugs that contain or are extracted from opium; *opioid* designates synthetic drugs, such as codeine, that have pharmacological properties similar to morphine or opium. *Narcotic* is a broader term for any drug, either synthetic or naturally occurring, with effects similar to those of opium and its derivatives, including meperidine (Demerol) and fentanyl (Duragesic). All new narcotics are compared to morphine, the standard, in terms of both potency and side effects.

Morphine and codeine act mainly on the CNS, where they produce a combination of depressing and stimulating effects. Both drugs increase smooth muscle tone and promote the contraction of smooth muscle. Morphine produces its potent analgesic effects by combining with receptor sites in the brain called *opioid receptors*.

In the CNS, five primary categories of opioid receptors have been identified: *mu, kappa, sigma, delta,* and *epsilon*. Mu, kappa, and sigma receptors are involved with analgesia. Opioids bind with receptors at various sites in the CNS to elicit their effects. They are capable of altering perception and emotional responses to pain.

Combining Analgesics

Acetaminophen and the NSAIDs are the first-line agents for management of mild to moderate pain. In patients with severe pain, these drugs may enhance the analgesic effects of narcotics. *Non-narcotic* analgesics have a ceiling effect, that is, increasing the dose of these drugs beyond a certain level does not result in any additional analgesia. For example, the ceiling dose of acetaminophen is at least 1000 mg. The long-term use of these agents is hindered by gastrointestinal and hematological side effects. If pain control is ineffective or if non-narcotic analgesics are poorly tolerated, then narcotic analgesics are indicated.

Combining drugs from a different class enables the clinician to improve pain relief without escalating the dose of the narcotic. Several combinations have proven effective, with the most effective combinations including a non-narcotic analgesic and a narcotic, such as the acetaminophen and hydrocodone combinations of **Norco®** and

Maxidone™. Narcotics have also been combined with *amphetamines* and *antihistamines*, but combinations with non-narcotic analgesics have the fewest side effects and are the combinations of choice for most people seeking relief from moderate to severe pain.

Using Opioids Effectively

As was mentioned previously, the analgesics that are currently available are safe and effective when the clinician properly selects and administers an analgesic based on the pharmacokinetics of the drug and the response of an individual patient. We also stated that the greatest abuse of narcotics is not inducing addiction, but rather not using a narcotic because of the *fear of addiction*.

To use opioid analgesics effectively requires that the physician balance pain relief with the undesirable side effects of nausea, vomiting, mental clouding, *sedation*, *constipation*, *tolerance*, and *physical dependence*. Part of this balance involves treating the side effects aggressively to facilitate dose titration and maximize analgesia. For example, using antiemetics and laxatives or stool softeners can ease some of the adverse effects of the opioids, allowing patients to remain on the drugs and maintain their analgesia.

Patients exhibit marked individual variation in the doses of opioids required to produce analgesia. In general, doses should be titrated to clinical effect or as limited by dose-related side effects. Unlike many other classes of drugs, opioids should not be administered "by cookbook," but rather by the logical path of stepwise administration and constant assessment of efficacy. Certain patients who use opioids require careful monitoring. Patients with special needs include the elderly—who may be at risk for falling because of the sedative effects of the opioids, as well as for constipation; those who exhibit drug-seeking behavior, for whom opioid use should, if warranted, be tightly monitored; and those with concurrent

The Non-narcotic Opioid

Tramadol (Ultram) is a unique, centrally acting synthetic analgesic that binds to opioid receptors. In addition to its effects on opioid receptors, tramadol weakly inhibits reuptake of norepinephrine and serotonin.

Tramadol is not a scheduled drug, but in 1996, its prescribing information was changed to add a warning of the risk of abuse among opioid-dependent patients, as well as the risk of withdrawal symptoms if therapy is suddenly discontinued. In addition, tramadol should not be taken when driving or operating machinery, when drinking alcoholic beverages, when using opiate-containing medications, or when there is a possibility that the patient may be pregnant.

Tramadol carries a risk of seizures that increases as dosages increase, particularly in patients who take tricyclic antidepressants, selective serotonin reuptake inhibitors, and opioids. Seizure risk may also be elevated by taking tramadol while using MAO inhibitors, neuroleptics, or other medications that increase susceptibility to seizures.

medical conditions, such as renal disease, in whom dosing must be carefully titrated to factor in any possible decreases in excretion.

Patients should generally receive analgesics on a schedule around the clock as opposed to waiting for a time when pain is at its apex. Administering analgesics as needed may result in frequent intervals of inadequate pain control. Remember (or quickly review) how the pain pathways work (Section 1). It is clear that keeping analgesics at therapeutic blood levels for the duration of pain works better than continually allowing the drug levels to drop. A good analogy is pushing a car that's out of gas: it takes a lot of effort to get the car rolling from a dead stop, but to keep it rolling takes much less effort.

Tolerance and Dependence

Tolerance refers to the diminished effectiveness of a drug upon repeated administration. The development of tolerance is dependent on the individual patient, and is therefore quite variable. However, in general, tolerance to the analgesic effect does tend to parallel tolerance to side effects like respiratory depression and sedation. Therefore, if a patient needs larger opioid doses for analgesia because of tolerance, he or she will usually also be tolerant to the respiratory depression, and will therefore be able to withstand the higher dose. On the other hand, many patients show less tolerance to the constipating effects of opioids, and at some point will require the use of laxatives.

Tolerance to the analgesic effects of opioids is generally managed by dose escalation. Patients receiving opioids regularly will frequently develop physiologic dependence in the sense that continued administration of opioids is required to prevent the development of symptoms of the withdrawal syndrome—severe perspiration, nasal stuffiness, diarrhea, hair standing on end, and tachycardia. This may occur following regular administration of opioids for as little as 14 days. Note that physical dependence is not the same as addiction. Addiction is a psychological syndrome characterized by compulsive drug-seeking behavior, generally associated with a desire to produce euphoria, not pain relief.

Physical dependence should rarely be a clinical problem; once a patient's pain subsides and it is desirable to diminish opioid administration, the withdrawal syndrome can be prevented by gradually tapering the dose over a period of several days.

Although physical dependence is common in patients receiving opioids for pain, addiction is quite rare. There is essentially no evidence that adequate administration of opioids for pain produces addiction. Indeed, there is reason to suppose that administering effective doses of opioids consistently on a schedule may produce less risk of abuse than administering them only when pain becomes unbearable.

Measuring Pain and Pain Relief

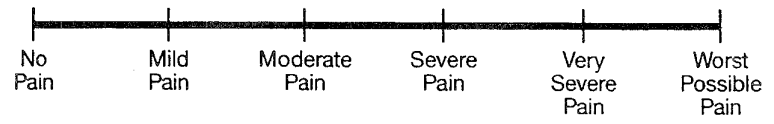
Pain measurement is vital in achieving adequate pain control, both before treatment to assess the type of intervention that should be instituted, and during administration to assess pain relief. Pain is an individual experience, and is not easily assessed by physicians, nurses, or other healthcare providers. Studies have shown that a patient's assessment of pain severity differs from that of the people caring for him or her; therefore, the most reliable indicator of the presence and severity of pain is the patient's own self-assessment.

Several methods of pain self-assessment have been developed. They include a variety of visual and numerical scales, along with other models that also account for the character of pain. Several common versions of these models are described below.

Simple Descriptive Pain Intensity Scale

Using a simple descriptive pain intensity scale, the patient assesses his pain based on a series of descriptors spaced equally along a straight line. The standard length of the line is 10 cm, and the descriptors range from "no pain" to the "worst possible pain." The patient places a mark on the line at the point that best describes the intensity of the pain he is feeling.

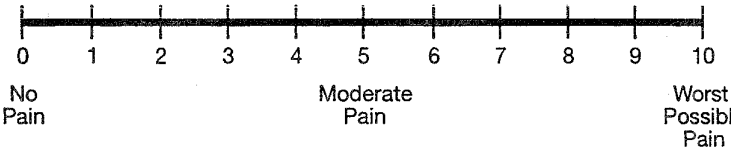
Figure 3.1 Simple Descriptive Pain Intensity Scale



Numerical Pain Intensity Scale

The numerical pain intensity scale is similar to the simple descriptive scale, but instead divides the line into 10 sections denoting increasing levels of pain. Three verbal descriptors are usually added, with "no pain" and "worst possible pain" on both ends and "moderate pain" in the middle. Again, the patient marks the line at the point that best describes the intensity of her pain.

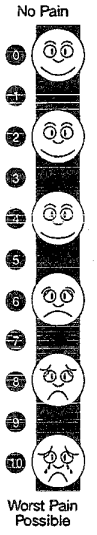
Figure 3.2 **Numerical Pain Intensity Scale**



Faces Rating Scale (Yale version)

The faces rating scale combines aspects of the first two rating scales. However, rather than using the verbal descriptors of the simple descriptive pain intensity scale, the faces rating scale uses depictions of six faces that show a range of emotion varying from happy to crying. This scale is especially appropriate for children and for patients with literacy or language barriers, but has been used with great success in many different types of patients.

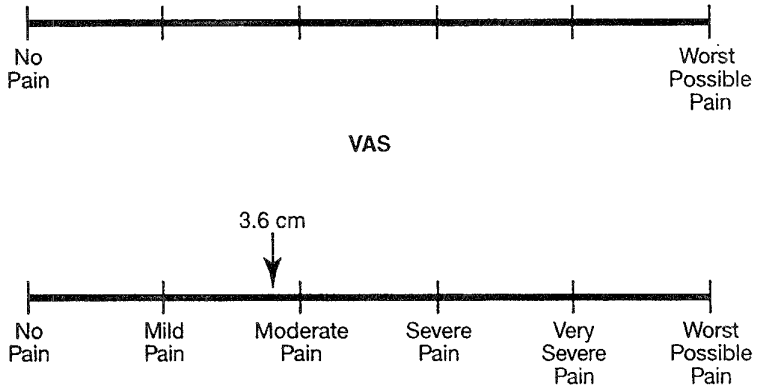
Figure 3.3



Visual Analog Scale

The visual analog scale, or VAS, is represented by an undivided line. Again, the standard length of the line is 10 cm, and the descriptors "no pain" and "worst possible pain" anchor the line at either end. Some VAS scales also use color to gauge pain intensity. The standard colors used are gradations of blue to describe no pain up to moderate pain, and gradations of red to describe moderate to severe pain.

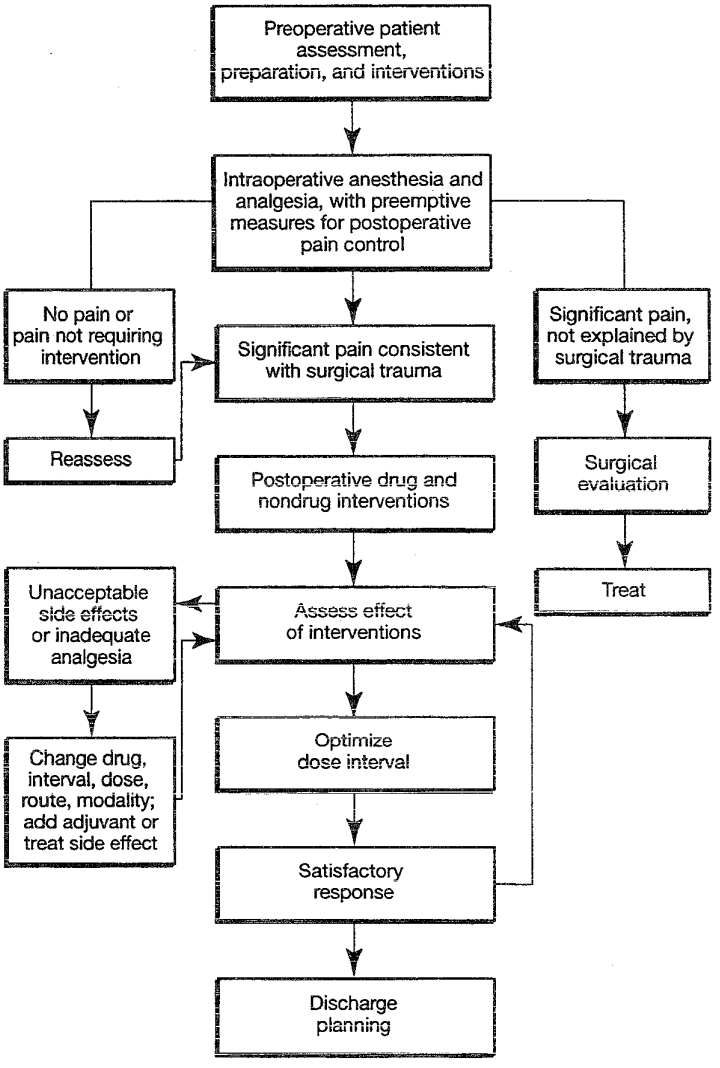
Figure 3.4 **Visual Analog Scale**



Putting It All Together: Managing Postoperative Pain

The U.S. Department of Health and Human Services has compiled a brief flow chart that encapsulates the steps necessary to gauge, implement, and monitor pain control following surgery. These steps are reproduced in Figure 3.5.

Figure 3.5 Postsurgical Pain Management



Section 3 Summary

- Pain can be controlled in 2 ways—by preventing prostaglandin synthesis at the site of injury or by blocking the perception of the pain by the brain.
- NSAIDs inhibit prostaglandin synthesis peripherally at the site of the injury, which results in effective anti-inflammatory activity.
- Acetaminophen produces its analgesic effect primarily by inhibiting prostaglandin synthesis in the CNS. Peripheral inhibition of prostaglandin synthesis is minimal, which may explain its lack of anti-inflammatory effects.
- The opioid analgesics, which have effects similar to that of morphine and opium, bind to opiate receptors in the brain and alter the perception of pain and emotional responses to pain.
- Adding non-narcotic analgesics to opioid analgesics increases the analgesic effects of the narcotic component. Combining opioid and nonopioid drugs enables the physician to improve pain relief without escalating the dose of the narcotic, thus reducing opioid side effects.
- Opioids are the mainstay of moderate to severe acute pain management. Moderate to moderately severe pain should normally be treated with opioids with or without a nonopioid analgesic (eg, acetaminophen).
- An essential component of pain management is careful assessment of efficacy through the use of pain intensity scales (eg, visual analog scales, numerical scales, etc.).

The Analgesic Category

Acetaminophen versus Aspirin

As discussed previously, patients exhibit marked variation in the doses of opioids required to produce analgesia. The same is true for non-narcotic analgesics. Acetaminophen, aspirin, and the other NSAIDs work in different ways in different people; aspirin and acetaminophen are not as interchangeable as many people believe.

First, as mentioned earlier, the two drugs work differently in the way they relieve pain; aspirin affects prostaglandin production both peripherally and in the CNS, whereas the majority of acetaminophen's activity appears confined to CNS enzymes.

Agents that strongly inhibit peripheral prostaglandin production, such as aspirin, decrease inflammation. Acetaminophen does not. Therefore, aspirin and other NSAIDs will help ease the discomfort caused by a swollen arthritic joint more than will acetaminophen. However, for other causes of pain—a mild injury or a sprained muscle in which there is not a great deal of inflammation—acetaminophen is as effective as aspirin, and is often the preferred option.

Other pros and cons of aspirin versus acetaminophen are listed in Table 4.1.

Table 4.1 Acetaminophen versus Aspirin

	Acetaminophen	*Aspirin*
Liver damage	Yes (doses >4 g/day)	No
Kidney damage	Yes (doses >4 g/day)	No
GI bleeding	No	Yes
Anticoagulant	Possible	Yes
Induces asthma	No	Yes
Contraindications	Alcohol consumption, hypersensitivity	Hypersensitivity, hemophilia, bleeding ulcers, hemorrhagic states

Other NSAIDs

Although other NSAIDs may be more effective than aspirin for pain control, they are more likely to cause damage to the liver and kidneys. Patients taking NSAIDs on a regular basis for arthritis or another inflammatory condition should undergo liver and renal function testing every 3 to 4 months. NSAIDs can also cause sodium retention, which is undesirable in cases where the patient is hypertensive or has a cardiac problem, such as congestive heart failure.

Even though NSAIDs are less irritating to the GI tract than aspirin, they should not be used if the patient has an active ulcer. If the patient is receiving anticoagulants such as warfarin, both aspirin and the NSAIDs can intensify the effect of the anticoagulant and increase the likelihood of bleeding.

At doses less than 4 grams daily, acetaminophen is a preferred analgesic option in patients with acute, noninflammatory pain, with a low incidence of side effects, excellent tolerability, fast onset of action, and good analgesic duration.

Opiate to Opioid

The individual members of the narcotic class differ with respect to potency, efficacy, and adverse effects. The pharmacokinetics of selected narcotics are listed in Table 4.2.

As can be seen in Table 4.2, hydrocodone—the opioid half of **Norco®** and **Maxidone™**—compares favorably with the other narcotics. Hydrocodone has a fast onset of action (10 to 30 minutes) and a long duration of action (4 to 6 hours), much like morphine, the standard by which other analgesics are measured. With moderate to moderately severe pain, these are probably the most important qualitites of an analgesic. Patients want pain relief fast and pain relief that lasts. Hydrocodone is an ideal opioid analgesic in this regard. A longer duration of action means physicians will not have to dose too frequently, which can increase the severity of side effects. Single-agent oxycodone (OxyContin) is available in a sustained-released formulation that may be dosed up to every 12 hours.

Table 4.2 **Pharmacokinetics of Selected Oral Narcotics**

Agent	*Time to Peak Effect (hr)*	*Half-life (hr)*	*Onset of Analgesia (min)*	*Duration of Analgesia (hr)*	*Equianalgesic Oral Dose (mg)*
Codeine	1-2	2.5-4	30-45	4	200
Hydrocodone	**0.5-1**	**3.8**	**10-30**	**4-6**	**30***
Hydromorphone	1.5-2	2.6-4	30	4	7.5
Meperidine	1-1.5	2.4-4	15	2-4	300
Morphine	1-2	2-3	10-30	4-5	60
Oxycodone	1	2-3	N/S	3-4	30
Propoxyphene napsylate	2	6-12	15-60	4-6	†

*Equianalgesic dose refers to hydrocodone in combination with a non-opioid analgesic. N/S = not specified
†Dose therapeutically equivalent to 10 mg of intramuscular morphine too toxic to administer.

Table 4.3 details the physiological effects of the selected narcotics, comparing both analgesia and side effects for each preparation.

Hydrocodone performs well compared with the other narcotics. Although opioids such as morphine, hydromorphone, meperidine, and oxycodone are thought to have greater analgesic efficacy than hydrocodone, they are associated with a greater risk of respiratory depression and greater abuse potential, hence their Schedule II designation (see next section). Hydrocodone has a faster onset of action, longer duration of action, and is better tolerated. The incidence of constipation, vomiting, and sedation is also less with hydrocodone than with morphine or oxycodone. Hydrocodone balances good analgesic efficacy with a relatively low incidence of side effects. Combine those characteristics with telephone prescribing convenience, and **Norco®** and **Maxidone™** come up winners.

Table 4.3 Properties of Oral Narcotic Analgesics

Drug	*Analgesia*	*Sedation*	*Nausea or Vomiting*	*Constipation*	*Euphoria*	*Comment*
Codeine	+	+++	++	++	+	Low potency
Hydrocodone	++	+	+	+	++	
Propoxyphene	+/-	+++	+	++	+	Rarely indicated
Hydromorphone	++	++	+	+	+++	
Oxycodone	+++	++	+	+	+++	
Pentazocine	++	+	+	+	+	CNS side effects

CNS, central nervous system.
Plus and minus symbols indicate *estimations* of degree of negative or positive effect.

Narcotic Scheduling

The Controlled Substances Act is designed to control the distribution of all depressant and stimulant drugs, including the opioids, barbiturates, and amphetamines. These drugs are required to bear the following warning:

Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

This act divides narcotics and other controlled drugs into five schedules:

Schedule I

Drugs in this schedule have a high potential for abuse and no currently accepted medical use in the United States. Drugs in this category include heroin, LSD, marijuana, mescaline, peyote, and about 80 opiates and opium derivatives.

Schedule II

Drugs in this schedule have a high potential for abuse with severe liability to cause psychic or physical dependence. Drugs here include morphine, codeine (as a sole ingredient), hydromorphone, meperidine, oxymorphone, oxycodone, dextroamphetamine, secobarbital, and methylphenidate. These drugs require triplicate written prescriptions and, in most states, cannot be refilled via the telephone.

Schedule III

Drugs in this schedule have a potential for abuse that is less than those in Schedules I and II. Drugs here include codeine and hydrocodone in combination with a non-narcotic agent, glutethimide, benzphetamine, chlorphentermine, and certain barbiturates.

Schedule IV

The drugs in this schedule have a low potential for abuse that leads only to limited physical or psychological dependence relative to drugs in Schedule III. Drugs here include phenobarbital, meprobamate, chloral hydrate, propoxyphene, and about 35 benzodiazepines, including diazepam, triazolam, and lorazepam.

Schedule V

Drugs in this class have a potential for abuse that is less than those in Schedule IV and consist of preparations containing moderate quantities of certain opioid drugs, generally for antitussive or antidiarrheal purposes.

Section 4 Summary

- Acetaminophen has several advantages over aspirin and other NSAIDs: it does not affect platelet aggregation and therefore does not affect bleeding time, an important consideration when prescribing analgesics in the postoperative setting. Acetaminophen also is not associated with gastrointestinal adverse effects.
- The recommended daily limit of acetaminophen is 4 g for acute pain therapy and 2.6 g for chronic therapy.
- Hydrocodone has a fast onset of action (10-30 minutes) and a long duration of analgesic effect (4-6 hours), comparable to that of oxycodone and codeine, the standard by which other opioid analgesics are measured.
- Hydrocodone has a lower risk of respiratory depression and lower abuse potential than most other opioids (eg, morphine, meperidine, hydromorphone, and oxycodone).
- Hydrocodone in combination with acetaminophen is a Schedule III narcotic and thus does not require a triplicate prescription.

Trends in the Analgesic Marketplace

Norco® and Maxidone™ in the Analgesic Marketplace

Five factors underlie the potential success of **Norco® 5/325, Norco® 7.5/325,** and **Maxidone™**:

1. Hydrocodone/acetaminophen is the number 1 prescribed drug in the United States. The market for narcotic analgesics is large and growing.
2. Opiate analgesics remain the standard by which other analgesics are measured, and hydrocodone is the first choice.
3. **Norco® 5/325, Norco® 7.5/325,** and **Maxidone™** are unique formulations.
4. Few competitive brands are heavily promoted.
5. You have established Watson, the largest producer of hydrocodone, in this market.

The alleviation of pain was one of medicine's earliest and most important objectives. Although the use of opiates was suppressed for a number of years based on the false belief that patients using the drugs appropriately for pain relief would necessarily become psychologically addicted and abuse them, the current, more enlightened attitude has led to a growing demand for these products. The 14 forms of narcotics currently available in the marketplace—including the opiates and their synthetic congeners, the opioids—are currently packaged into more than 80 different labels and formulations, many in combination with non-narcotic analgesics, primarily acetaminophen and aspirin.

Many of these products duplicate one another's formulation, and rely on price and distribution for their market share. Products with unique formulations based on medical rationale have a real opportunity to establish themselves. With the incidence of acetaminophen toxicity being an area of concern for many in the medical community, there is a very real medical rationale for all of the low-dose acetaminophen **Norco®** formulations. Conversely, many physicians are looking for higher-strength analgesics to treat patients with higher degrees of pain. **Maxidone™** offers these physicians the highest strength combination of hydrocodone and acetaminophen available.

Narcotic Sales Are Increasing

The number of prescriptions for hydrocodone/acetaminophen combinations, already the most prescribed product in the United States, continues to increase. As can be seen in Table 5.1, in 1999, the class grew by 12% in overall prescriptions. This combination is dispensed at a rate of two prescriptions per second, over 70,000,000 prescriptions per year. As you are well aware, **Norco® 10/325** benefited greatly from the growth of this market. In 1999, **Norco® 10/325** prescriptions grew by an astounding 110%! This set the stage for 2000, when **Norco® 10/325** led the

hydrocodone/acetaminophen market in dollar sales. The increase in prescriptions is indicative of a healthy market. In short, **Norco® 5/325, Norco® 7.5/325,** and **Maxidone™** are being introduced into the same growing market that was so receptive to **Norco® 10/325**—one that should continue to respond favorably to products with unique features and benefits.

Table 5.1 **Total Prescriptions, Hydrocodone/Acetaminophen Combinations, 1998-1999 (000)**

Hydrocodone Combinations	1998	1999	% Change
5 mg	30,572	34,360	+12%
7.5 mg	22,367	24,387	+9%
10 mg	6,884	8,389	+22%
Total	59,823	67,136	+12%

A number of factors have combined to stimulate the market for narcotic analgesics:

- Recognition in the medical community that the fear of prescribing opiates was partially a response to social pressures, and that some patients were being undermedicated for pain...sometimes with dire results
- Realization that fear of addiction due to even chronic use of narcotics was largely unwarranted
- Understanding that prescription drug-related abuse problems could be dealt with through physician education and better control of prescriptions
- Institution of the stringent cost-effectiveness guidelines so characteristic of medical practice today
- Normal population growth

Market Trends Favor Success for Norco® and Maxidone™

- Physician attitudes toward the opioids have become more favorable.
- Physicians are treating pain more vigorously.
- Combination opioid analgesics are still the cost-effective and economical way to treat many types of pain.
- **Norco®** and **Maxidone™** are competitively priced.

The Market for Norco® Is Substantial

Physicians are writing more and more of the 5 mg and 7.5 mg hydrocodone combinations, despite introductions of "new" products. In 1978, Vicodin was launched. In 1988, Lortab, the first 7.5 mg combination, came on the market, and was soon followed by Vicodin ES. These successful product introductions, and others that followed, are still considered cornerstones of pain therapy. Currently, the 5 mg combinations are still the most widely prescribed, but the hydrocodone market has continued to expand for the 7.5 mg formulations at an impressive rate. Moreover, both segments have grown significantly with little promotional support from the pharmaceutical manufacturers of the products that compete with the two newest **Norco®** formulations.

The 5-mg segment of the market remains the steady leader, capturing 51% of all hydrocodone/acetaminophen prescriptions. As Table 5.1 illustrates, the segment continues to see double-digit increases in prescriptions. As the product labeling allows physicians to prescribe 1 or 2 tablets every 4 to 6 hours, as needed, the flexibility of titration is unmatched by the higher strength hydrocodone products. **Norco® 5/325** will compete primarily with Vicodin and Lortab 5/500 and Zydone 5/400.

The 7.5-mg segment into which **Norco® 7.5/325** will enter grew at a rate of 9% in total prescriptions in 1999. At present, this segment consists of Vicodin ES, Lorcet Plus, Zydone 7.5/400, and Lortab 7.5. The market leader is Vicodin ES.

The Market for Maxidone™ Is Growing

The 10-mg segment grew at the impressive rate of 22% in total prescriptions in 1999. Products that compete with **Maxidone™** include **Norco® 10/325,** Lorcet 10, Lortab 10, Zydone 10/400, and Vicodin HP.

As table 5.1 illustrates, growth of the 10-mg segment outpaced the market considerably. As mentioned previously, some of this growth can be attributed to **Norco® 10/325.** Prescriptions for the 10/650 combination grew 20%, accounting for 56% of all prescriptions in this segment.

In addition to 10-mg hydrocodone products, **Maxidone™** will compete with high-strength acetaminophen products that contain less than 10 mg of hydrocodone, such as Vicodin ES (7.5/750). Table 5.2 illustrates that high-strength acetaminophen products grew 12% in 1999, accounting for 33% of all hydrocodone/acetaminophen prescriptions. The 7.5/750 strength alone grew 14% and owns 19% of the market.

Table 5.2 **Total Prescriptions for Hydrocodone Combination Products Containing at Least 650 mg of Acetaminophen (000)**

Dose	1998	1999	Increase/Decrease
7.5/650	3,329	3,365	+1%
7.5/750	9,836	11,197	+14%
10/650	3,952	4,738	+20%
10/660	244	205	-16%
Total	17,361	19,505	+12%

Norco® and Maxidone™ Mean Unquestioned Efficacy at the Right Price

Rather than having to establish the efficacy of a new medication, your challenge is to alert physicians to a unique and especially beneficial dosage of a proven analgesic combination. The efficacy of hydrocodone/acetaminophen combinations is accepted: physicians write more prescriptions for hydrocodone/acetaminophen than they do for any other product. Lorcet and Vicodin ES have already successfully established the validity of high-dose combinations. **Maxidone™** will build on physician demand for these products by offering the highest strength hydrocodone/acetaminophen combination available. **Norco® 10/325** has proven the need for low-dose acetaminophen in combination with popular strengths of hydrocodone. For those physicians concerned about chronic acetaminophen, **Norco® 5/325** and **Norco® 7.5/325** offer low-acetaminophen combinations with the most popularly prescribed strengths of hydrocodone.

And these products will be competitively priced.

In today's cost-conscious climate, competitively priced products are appreciated by clinicians and pharmacists. **Norco®** and **Maxidone™** are priced competitively to most other hydrocodone/acetaminophen products. Moreover, the suggested wholesale price (SWP) of **Norco® 7.5/325** is 25% less than that of Vicoprofen. The tables that follow show the SWPs of **Norco®, Maxidone™**, and their principal competitors. As you can see, price will not pose an obstacle in getting physicians to write them, or pharmacies to order them.

Table 5.3 SWP* by Brand and Manufacturer, Hydrocodone Combination Products

Manufacturer	Brand, Dosage, and Combination	SWP Bottle/100
Endo	Zydone Tablets 5/400 acetaminophen	$53.51
	Zydone Tablets 7.5/400 acetaminophen	$59.02
	Zydone Tablets 10/400 acetaminophen	$71.92
Forest	Lorcet HD Capsules 5/500 acetaminophen	$35.71
	Lorcet Plus Tablets 7.5/650 acetaminophen	$92.66
	Lorcet Tablets 10/650 acetaminophen	$130.34
Knoll	Vicodin Tablets 5/500 acetaminophen	$52.93
	Vicodin ES Tablets 7.5/750 acetaminophen	$58.37
	Vicodin HP Tablets 10/660 acetaminophen	$66.44
	Vicoprofen Tablets 7.5/200 ibuprofen	$99.06
Mallinckrodt	Anexsia Tablets 5/500 acetaminophen	$50.90
	Anexsia Tablets 7.5/650 acetaminophen	$64.57
	Anexsia Tablets 10/660 acetaminophen	$81.12
UCB Pharma	Lortab Tablets 5/500 acetaminophen	$68.87
	Lortab Tablets 7.5/500 acetaminophen	$76.28
	Lortab Tablets 10/500 acetaminophen	$79.97
Watson	**Norco® Tablets 5/325 acetaminophen**	**$65.00**
	Norco® Tablets 7.5/325 acetaminophen	**$74.60**
	Norco® Tablets 10/325 acetaminophen	**$85.60**
	Maxidone™ Tablets 10/750 acetaminophen	**$91.10**

Table 5.4 SWP* by Brand and Manufacturer, Oxycodone Combination Products

Manufacturer	Brand, Dosage, and Combination	SWP Bottle/100
Endo	Percocet Tablets 5/325 acetaminophen	$96.88
	Percodan Tablets 4.50/.38/325 aspirin	$101.06
McNeil	Tylox Capsules 5/500 acetaminophen	$95.29
Roxane	Roxicet Tablets 5/500 acetaminophen	$57.60

Table 5.5 SWP* by Brand and Manufacturer, Codeine Combination Products

Manufacturer	Brand, Dosage, and Combination	SWP Bottle/100
McNeil	Tylenol w/Codeine #4 Tablets 60/300 acetaminophen	$70.97
	Tylenol w/Codeine #3 Tablets 30/300 acetaminophen	$40.16
Robins	Phenaphen w/Codeine #4 Capsules 60/325 acetaminophen	$81.68

* December 2000 prices

Section 5 Summary

- Hydrocodone/acetaminophen is the number 1 prescribed drug in the United States, with >85 million prescriptions written each year. This number is steadily growing at a rate of 15%.
- Physicians are increasingly prescribing high-dose hydrocodone combination products.
- Physicians prescribe products containing >650 mg acetaminophen 15 times more often than they prescribe products containing <650 mg acetaminophen.
- **Norco®** and **Maxidone™** are unique formulations.
- **Norco®** combines the two most commonly prescribed doses of hydrocodone (5 mg and 7.5 mg) with a lower dose of acetaminophen (325 mg).
- **Maxidone™** responds to the trend among physicians to prescribe more potent hydrocodone/acetaminophen combinations.
- Both **Maxidone™** and **Norco®** are competitively priced.

Positioning Norco®

Key Selling Points for Norco®

- Hydrocodone/acetaminophen is the number 1 prescribed drug in the United States, with >85 million prescriptions written each year. This number is steadily growing at a rate of 15%.
- **Norco®** combines the two most commonly prescribed doses of hydrocodone (5 mg and 7.5 mg) with a lower dose of acetaminophen (325 mg).
- Hydrocodone has a fast onset of action (10 to 30 minutes) and relatively long duration of action (4 to 6 hours), comparable to that of oxycodone and codeine, the standard by which opioid analgesics are measured.
- The potential for physical dependence is lower with hydrocodone than with most other opioids. In combination with acetaminophen, hydrocodone is a Schedule III narcotic and does not require a triplicate prescription. **Norco®** can be prescribed over the phone in most states.
- Acetaminophen is the preferred non-narcotic analgesic for pain that does not have a significant inflammatory component. It does not affect bleeding time and is not associated with gastrointestinal adverse events, unlike ibuprofen, aspirin, and other nonsteroidal anti-inflammatory drugs.
- The low-dose acetaminophen formulations of **Norco®** allow doctors to prescribe hydrocodone/acetaminophen without being restricted by the 4-g recommended daily limit of acetaminophen. With **Norco® 5/325**, doctors can prescribe up to 12 tablets without reaching the 4-g daily limit of acetaminophen.
- **Norco®** can be prescribed for chronic pain as well, since even at a dosage of 6 tablets per day, the 2.6 recommended daily limit for *chronic* acetaminophen therapy will not be reached.
- Some patients may benefit from lower-dose acetaminophen in a hydrocodone/acetaminophen combination product, including elderly patients in whom hepatic and renal function is often diminished, persons with low food intake or poor nutrition, and alcoholic patients.
- **Norco®** may reduce the chances of acetaminophen toxicity since patients may be taking OTC medications that contain acetaminophen, inadvertently increasing their daily acetaminophen intake.
- The small tablet size of **Norco®** may make it easier for certain patients to swallow, especially those who have undergone oral surgery.
- **Norco®** is competitively priced.

Strategy and Tactics

Professional Plan

1. Objectives

   - Expand our product line in the rapidly growing hydrocodone market
   - Capture a substantial portion of the lucrative 5-mg and 7.5-mg hydrocodone segments
   - Capitalize on the growing awareness of acetaminophen toxicity

2. Immediate Marketing Goal

   - Build brand awareness by showing that:
     - **Norco®** formulations are unique combinations of popular strengths of hydrocodone and a low dose of acetaminophen
     - The hydrocodone/lower-dose acetaminophen formulations have clinical and dosing advantages
     - The potential for exceeding the 4-gram daily limit is lower with the two **Norco®** combinations
     - **Norco®** formulations are excellent choices for chronic use
     - The side-effect profile of either strength is favorable
     - **Norco®** has the smallest tablet of any hydrocodone combination in its class, an important consideration for certain patients
     - All **Norco®** formulations have the convenience of Schedule III prescribing
     - The cost of the two **Norco®** combinations is competitive

3. Strategy

   - Initiate a high-profile message using a mixture of proven tactics to increase the trial and usage of **Norco® 5/325** and **Norco® 7.5/325**
   - Target a limited number of high-prescribing medical specialists:
     - Family Practice/General Practice
     - Internal Medicine
     - Emergency Medicine
     - Orthopedic Surgeons

- Pain Management
- Neurologists
- Surgeons

• Target pharmacists

4. Tactics

• Selling tools directed to the physician

- Detail aids
- File cards
- Leave-behind premiums—pens, pads, etc.
- Samples
- Educational materials

• Selling tools directed to the trade buyer

- Fact sheets/sell sheets

• Journal Advertising

• Direct Mail

- MD mail
- Retail pharmacy mail

The Norco® Advantage

Norco® 10/325 launched at a very opportune time, when the medical community began to recognize that acetaminophen was not as benign as once thought and narcotic analgesics—when appropriately prescribed—were not as problematic as originally believed. **Norco® 10/325** capitalized on this timing, and set the stage for **Norco® 5/325** and **Norco® 7.5/325** to build on the success of this product. What sets **Norco®** apart from the competition—the **Norco®** advantage—is the lowest level of acetaminophen available. Let's take a closer look...

High Doses of Acetaminophen in Combination Products Aren't Always Advisable or Necessary

For some types of pain, the prostaglandin inhibition of high-dose acetaminophen can be very beneficial, and high-dose combination prescriptions are, therefore, very appropriate. But when a physician is prescribing a high-dose combination primarily for the opiate activity of the hydrocodone, the high dose of acetaminophen may actually become a limiting factor.

Hydrocodone can be dosed initially at 10 mg every 3 to 4 hours. In fact, in the clinical guidelines, *Acute Pain Management in Adults: Operative Procedures*, the U.S. Department of Health and Human Services (DHHS) states that up to 10 mg of oral hydrocodone should be dosed every 3 to 4 hours for postoperative pain in patients greater than 110 pounds. Its only limiting factors are side effects, such as respiratory depression, which were covered in section 3. **This means that the high-dose acetaminophen in some combinations may be limiting the amount of hydrocodone that can be prescribed.** And the high-dose acetaminophen may therefore be limiting the patient's pain relief. For example, if a physician wants to follow the DHHS recommendations, he or she can still only prescribe a maximum of six tablets of the 10-mg or 7.5-mg products with either 650 or 660 mg of acetaminophen (Anexsia, Lorcet, Vicodin) or eight tablets of Lortab 10. **Although this is not in our labeling,** if a physician wanted to prescribe a higher dose of hydrocodone in accordance with the DHHS recommendations, he or she could prescribe up to 12 **Norco® 5/325** or **Norco® 7.5/325** tablets in a day before the 4-gram limit of acetaminophen is reached (see Table 6.1).

On the other hand, you may ask, "Why not just give more acetaminophen along with the hydrocodone?"

Table 6.1 Number of Pills Needed to Achieve the 4-g Limit of Acetaminophen Based on Single-Pill Dosage

Acetaminophen Dosage (mg)	*Number of Pills Needed to Achieve 4-g Daily Limit*
325	12
500	8
650–660	6
750	5

Acetaminophen Toxicity: A Growing Concern

It has been more than 45 years since acetaminophen was introduced and more than 35 years since it became available OTC. Alone or in combination with other analgesics, acetaminophen has become one of the most widely used analgesics, and is now a major ingredient of more than 100 OTC medications. Although its image is a benign one, it has become the most common cause of both accidental and intentional poisoning requiring hospitalization. Nearly 65,000 incidents of acetaminophen poisoning involving combination products were reported in 1998. Through the literature, the medical community is fast becoming aware of the magnitude of this danger.

Acetaminophen is naturally toxic to the liver but is rarely dangerous at doses below the recommended daily limit of 4 grams for adults. However, some cases of liver toxicity have been reported in patients taking as little as 3 grams of acetaminophen per day for extended periods. This toxic effect may even occur at lower doses in patients who regularly use or abuse alcohol and in patients who are anorexic or have very low food intake. These patients, who may not admit to heavy alcohol use or bulimic behaviors when asked by their physician, are at high risk for liver toxicity when they use acetaminophen. Patients who are taking anticoagulant drugs such as warfarin may be at risk of additional bleeding when taking large doses of acetaminophen. In addition, patients who are taking antiseizure drugs such as phenobarbital or antituberculosis drugs such as isoniazid may also be at increased risk for acetaminophen toxicity since these drugs induce the P450 enzyme that breaks down acetaminophen into its toxic metabolite.

The cytochromes P450 are a family of enzymes that metabolize drugs in the liver so that they can be more easily eliminated from the body. Different enzymes of the P450 family metabolize different drugs. Acetaminophen is metabolized by one of the P450 enzymes into a toxic and reactive byproduct. Under normal conditions, this byproduct is immediately detoxified when it binds to a molecule called glutathione. Some drugs, such as isoniazid and ethanol, can induce or "turn on" this P450 enzyme to

increase the metabolism of acetaminophen (see Table 6.2). This increased metabolism causes the toxic metabolite to accumulate in the liver. Some of these drugs may also decrease the supply of glutathione, which again causes a buildup of the toxic metabolite.

Chronic use of large doses of acetaminophen has also been linked to the risk of end-stage kidney disease, and the risk is related to the dose of acetaminophen consumed over a year. The daily limit for acetaminophen in chronic pain therapy is 2.6 g. Thus, acetaminophen is an effective and relatively safe drug at doses less than 4 grams daily, but the risk of toxicity increases when doses regularly exceed this limit.

Table 6.2 Inducers of P450 Enzymes

- Carbamazepine (Tegretol)
- Dexamethasone (Decadron)
- Phenobarbital
- Phenytoin (Dilantin)
- Rifampin (Rifadin, Rimactane)
- Omeprazole (Prilosec)
- Ethanol
- Isoniazid (Laniazid)

Often patients (and physicians) are not aware of all the potential sources of acetaminophen in the medicine cabinet. Many OTC allergy, sinus, cold, and flu medications contain large doses of acetaminophen. Patients who are on hydrocodone/acetaminophen medication for pain may still consume these acetaminophen-containing OTC products when they have allergies or colds, unaware that they are exceeding the 4-gram daily limit of acetaminophen. Thus, a patient taking the maximum dose of a combination hydrocodone/higher-dose acetaminophen product along with an OTC medication that contains acetaminophen may be ingesting as much as 7.9 grams of acetaminophen a day! That's almost twice the daily recommended dose. In 1993, Csete and Sullivan reported on three patients who suffered severe liver damage after they took Vicodin for postoperative pain and additional pure acetaminophen. These authors noted that these patients, two of whom died of liver failure, were never informed of the dangers of taking these two drugs at the same time. They added that "*whenever the dose of [a hydrocodone/acetaminophen combination] is escalated for pain relief, careful consideration must be given to the total amount of acetaminophen that the patient will receive.*"

Patients may unintentionally overdose on acetaminophen by dosing too frequently (eg, every 2 hours instead of every 4 hours) or by taking more than 1 g per dose to relieve persistent pain. Many patients are unaware of the 4-g daily dosing limit or the toxic effects of exceeding this limit. For more information on this subject, refer

to the *New England Journal of Medicine* in section 12. Those under the influence of alcohol may also overdose on acetaminophen due to clouded sensorium.

When it comes to pain relief, **Norco®** provides patients and physicians with a higher margin of safety. At the usual daily dose, **Norco® 5/325** and **Norco® 7.5/325** provide high levels of hydrocodone but just 1.95 grams of acetaminophen, well below the recommended maximum daily dose of 4 grams and even below the 2.6-g limit for chronic therapy. A patient taking the usual six tablets of **Norco®** and four acetaminophen-containing allergy tablets, for example, would still be within the 4-gram daily limit of acetaminophen. When physicians prescribe **Norco®**, they can be less concerned about whether their patients are taking OTC medications that contain acetaminophen or have other risk factors which may make them susceptible to acetaminophen toxicity.

Table 6.1 clearly illustrates the potential for prescribing more hydrocodone and less acetaminophen when the combination contains only 325 mg of acetaminophen. With either the **Norco® 5/325** or **Norco® 7.5/325** combination, the physician can prescribe the most popular strengths of a CIII narcotic without exceeding the 4-gram daily limit for acetaminophen.

Taking Excessive Doses of Acetaminophen, Especially Chronically, Is Inadvisable for Many Patients

As noted in the previous sections, in patients with hepatic or renal insufficiencies, as well as alcoholics, doses of acetaminophen should be carefully monitored. Continual, concurrent administration of such commonly prescribed medications as barbiturates, phenothiazines, and warfarin may also interact with high doses of acetaminophen. It should also be pointed out that the elderly, a significant segment of the overall population, normally have some degree of diminished liver or kidney function, or both. Members of this group should certainly be considered for a low-dose acetaminophen combination.

In general, it may well be prudent for the physician who wants to prescribe a potent acetaminophen/opioid combination to specify one with a lower dose of acetaminophen—unless he or she specifically wants the higher dose. Obviously, if a physician is aware that acetaminophen is contraindicated for a patient, it won't be prescribed. But physicians may not always be aware of such contraindications. All of these factors would certainly suggest that there is a definite place for **Norco®** in the physician's analgesic armamentarium.

Norco® Has a Lower Level of Acetaminophen Than Any Other Branded Hydrocodone/Acetaminophen Combination Products

In prescribing a potent oral opioid/acetaminophen combination, physicians currently have a laundry list to choose from.

The currently available combinations all have a minimum of 400 mg of hydrocodone/acetaminophen. Although equianalgesic oxycodone combinations do have the same low dose of acetaminophen as **Norco®**, they are CII drugs, with

Table 6.3 Current High-Dose Oral Opiate Combinations

Manufacturer	*Brand and Dosage*
	Hydrocodone/Acetaminophen
Endo	Zydone 10/400
	Zydone 7.5/400
	Zydone 5/400
Forest	Lorcet 10/650
	Lorcet Plus 7.5/650
Knoll	Vicodin HP 10/660
	Vicodin ES 7.5/750
	Vicoprofen 7.5/200 (ibuprofen)
Mallinckrodt	Anexsia 7.5/650
	Anexsia 10/660
UCB Pharma	Lortab 7.5/500, 10/500
Watson	**Norco® 10/325**
	Norco® 7.5/325
	Norco® 5/325
	Maxidone™ 10/750
	Oxycodone/Acetaminophen
Endo	Percocet 5/325
Ortho-McNeil	Tylox 5/500
Roxane	Roxicet 5/500 Caplets
	Roxilox Capsules 5/500
	Codeine/Acetaminophen
McNeil	Tylenol/codeine #4 60/300
	Tylenol/codeine #3 30/300

the extra prescribing restrictions, side effects, and abuse potential associated with that designation. Moreover, **Norco®** offers hydrocodone at a dosage that has been well received by the medical profession, and acetaminophen at a dosage that is in agreement with current medical thinking.

Norco® is a unique product with a unique selling point—the ingredients of success.

Competitive Products

This section highlights the competition by product.

Table 6.4 Lortab 5/500 • Vicodin 5/500

Manufacturers:	UCB/Knoll
Formulations:	5 mg hydrocodone/500 mg acetaminophen
Narcotic Control Schedule:	CIII
Indication:	Moderate to moderately severe pain

The Norco® 5/325 Advantage

- Less acetaminophen means less potential for exceeding the recommended 4-gram maximum daily dose of acetaminophen
- Smaller tablet size compared with other hydrocodone/acetaminophen combinations may make it easier to swallow, especially for oral surgery patients
- Vicodin 5/500 has a daily dose limit of 8 tablets whereas 12 **Norco® 5/325** tablets may be prescribed per day
- **Norco® 5/325** is less expensive than Lortab 5/500

Table 6.5 Lorcet Plus • Lortab 7.5/500 • Vicodin ES • Vicoprofen

Manufacturers:	Forest/UCB/Knoll
Formulations:	7.5 mg hydrocodone/650, 500, or 750 mg acetaminophen or 200 mg ibuprofen
Narcotic Control Schedule:	CIII
Indication:	Moderate to moderately severe pain

The Norco® 7.5/325 Advantage

- Less acetaminophen means less potential for exceeding the recommended 4-gram maximum daily dose of acetaminophen
- Smaller tablet size compared with other hydrocodone/acetaminophen combinations
- Vicoprofen has more side effects including GI bleeding and has many listed drug interactions
- Vicoprofen has a daily dose limit of 5 tablets
- Vicoprofen is the most expensive oral 7.5 mg hydrocodone combination product
- Vicodin ES has a daily dose limit of 5 tablets
- **Norco® 7.5/325** is less expensive than Lortab 7.5/500 or Lorcet Plus
- **Norco® 7.5/325** therapy is not limited, whereas Vicoprofen therapy is restricted to 10 days or less

Table 6.6 Percocet • Percodan

Manufacturer:	DuPont
Formulation:	5 mg oxycodone/325 mg acetaminophen
Narcotic Control Schedule:	CII
Indication:	Moderate to moderately severe pain
Variants:	Percodan 5 mg oxycodone/325 mg aspirin

The Norco® Advantage

- Similar analgesic potency—both strengths indicated for moderate to moderately severe pain
- Two formulations make more precise titration possible
- Longer duration of action
- A CIII designation—less potential for abuse
- Prescribing convenience—a CIII designation, refills, convenience of phone-in prescriptions, no triplicate forms
- Competitively priced

Table 6.7 Tylenol with Codeine

Manufacturer:	McNeil
Formulation:	#2-15 mg codeine/300 mg acetaminophen, #3-30 mg codeine/ 300 mg acetaminophen, #4-60 mg codeine/300 mg acetaminophen
Narcotic Control Schedule:	CIII
Indication:	Mild to moderately severe pain
Variants:	Tylox 5 mg oxycodone/500 mg acetaminophen (CII)

The Norco® Advantage

- Provides faster analgesia, with an onset of 10 to 30 minutes versus 30 to 45 minutes for codeine. Less time to wait for relief means fewer doses, less discomfort. More potent, and a longer duration of action.
- A more favorable side effect profile (less CNS effects such as lightheadedness and sedation and less GI effects such as nausea and vomiting) than codeine at higher doses.

Section 6 Summary

- The low-dose acetaminophen formulations of **Norco®** allow doctors to prescribe hydrocodone/acetaminophen without being restricted by the 4-g recommended daily limit of acetaminophen. With **Norco® 5/325**, doctors can prescribe up to 12 tablets without reaching the 4-g daily limit of acetaminophen.
- **Norco®** can be prescribed for chronic pain as well, since even at a dosage of 6 tablets per day, the 2.6-g recommended daily limit for *chronic* acetaminophen therapy will not be reached.
- Some patients may benefit from lower-dose acetaminophen in a hydrocodone/acetaminophen combination product, including elderly patients in whom hepatic and renal function is often diminished, persons with low food intake or poor nutrition, and alcoholic patients.
- **Norco®** may reduce the chances of acetaminophen toxicity since patients may be taking OTC medications that contain acetaminophen, inadvertently increasing their daily acetaminophen intake.
- The small tablet size of **Norco®** may make it easier for certain patients to swallow, especially those who have undergone oral surgery.
- **Norco®** is competitively priced.

Positioning Maxidone™

Key Selling Points for Maxidone™

- Doctors are increasingly prescribing high-dose hydrocodone and high-dose acetaminophen opioid/nonopioid combinations.
- Doctors prescribe combinations containing >650 mg acetaminophen 15 times more often than they do products containing <500 mg.
- The number of prescriptions for 10-mg hydrocodone combinations grew by 23% and the number of prescriptions for high-dose acetaminophen products grew by 16%.
- **Maxidone™** contains the highest dose of hydrocodone and the highest dose of acetaminophen available in a single tablet.
- **Maxidone™** provides strong analgesia without the serious side effects associated with other strong opioid combinations (eg, oxycodone/acetaminophen).
- **Maxidone™** is potentially the strongest analgesic available without a triplicate prescription.
- The 750 mg of acetaminophen in each tablet is below the ceiling dose of 1000 mg for acetaminophen and thus provides more analgesia than lower doses of acetaminophen.
- At the maximum daily dose of 5 tablets, **Maxidone™** still remains within the 4-gram daily recommended limit for acetaminophen.
- The AHCPR guidelines recommend a starting dose of 10 mg hydrocodone in patients weighing >110 lbs for postoperative pain.
- **Maxidone™** is competitively priced to other brands in its class.

Strategy and Tactics

Professional Plan

1. Objectives
   - Convert a substantial portion of the current **Norco® 10/325** subscribers to **Maxidone™**
   - Expand our product line in the rapidly growing 10-mg segment of the hydrocodone market
   - Capitalize on the growth of high-potency analgesic products

2. Immediate Marketing Goal

- Build brand awareness by showing that:
  - There is now a full-strength oral hydrocodone formulation as an alternative to Schedule II products
  - The **Maxidone™** formulation (10/750) is unique
  - **Maxidone™** delivers the highest strength of hydrocodone and highest strength of acetaminophen available in a single tablet
  - **Maxidone™** contains 33% more hydrocodone per tablet than Vicodin ES
  - The cost of **Maxidone™** is competitive
  - **Maxidone™** may be appropriate for patients who have moderately severe pain which may not respond to smaller analgesic doses
- Emphasize to physicians that:
  - The AHCPR guidelines recommend a starting dose of 10 mg hydrocodone in patients weighing >110 lbs
  - The larger dose of acetaminophen raises the level of analgesia compared with smaller doses, but remains within the ceiling dose of 1000 mg
  - At the maximum daily dose of 5 tablets, the acetaminophen content of **Maxidone™** remains within the 4-gram daily recommended limit

3. Strategy

- Initiate a high-profile message using a mixture of proven tactics to increase the trial and usage of **Maxidone™**
- Target a limited number of high-prescribing medical specialists:
  - Family Practice/General Practice
  - Internal Medicine
  - Emergency Medicine
  - Orthopedic Surgeons
  - Pain Management
  - Neurologists
  - Surgeons
- Target pharmacists

4. Tactics

- Selling tools directed to the physician
  - Detail aids
  - File cards
  - Leave-behind premiums – pens, pads, mugs, etc.
  - Samples
- Selling tools directed to the trade buyer
  - Fact sheets/sell sheets
- Journal Advertising
- Direct Mail
  - MD mailer
  - PharmAlert mailer

The Maxidone™ Advantage

The launch of **Maxidone™** comes at a time when the higher dose 10-mg hydrocodone combinations are experiencing tremendous growth. In 1999, the number of prescriptions for 10-mg hydrocodone products grew by 22% compared with the previous year. More and more, physicians are prescribing the high-dose hydrocodone combinations, perhaps in response to the guidelines of the AHCPR, which recommend a starting dose of 10 mg hydrocodone in patients >110 lbs, or as part of a growing trend to treat pain more aggressively.

Physicians are also increasingly prescribing products with higher doses of acetaminophen, as demonstrated by the growth in the numbers of prescriptions of 7.5/750 (Vicodin ES) and 10/650 (Lorcet) hydrocodone/acetaminophen combinations. In fact, physicians prescribe combination opioids with at least 650 mg of acetaminophen almost 15 times more often than they prescribe products that contain less than 500 mg (Figure 7.1). **Maxidone™** is a unique formulation that responds to both these prescribing trends. It contains the highest dose of hydrocodone and the highest dose of acetaminophen available in a combination tablet (Table 7.1).

Figure 7.1 **Total Prescriptions: Select Hydrocodone/Acetaminophen Combinations**

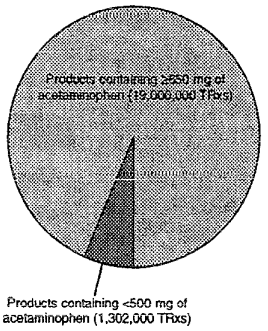


Table 7.1 **Current High-Dose Hydrocodone/Acetaminophen Combinations**

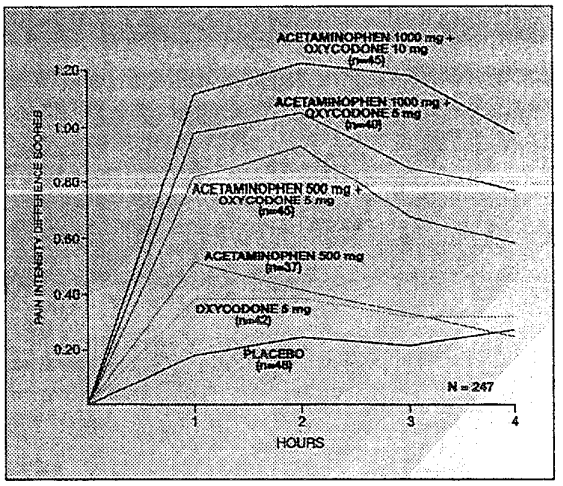
Manufacturer	*Brand and Dosage*
Endo	Zydone 7.5/400, 10/400
Forest	Lorcet Plus 7.5/650, Lorcet 10/650
Knoll	Vicodin HP 10/660, Vicodin ES 7.5/750
Mallinckrodt	Anexsia 7.5/650, 10/660
UCB Pharma	Lortab 7.5/500, 10/500
Watson	**Norco 7.5/325, 10/325, Maxidone 10/750**

Overcoming Barriers without Crossing the Limits

Since hydrocodone, a full agonist opioid, is not subject to ceiling effects, a larger dose can be expected to produce higher levels of pain relief than a lower dose. Per tablet, **Maxidone™** contains 33% more hydrocodone than Vicodin ES. So, it follows that with each dose, **Maxidone™** can be expected to produce more profound analgesia than Vicodin ES, although this has not been proven in head-to-head clinical studies. As shown in Figure 7.2, for example, increasing the dose of oxycodone from 5 mg to 10 mg while keeping the acetaminophen dose fixed results in increased analgesia as measured by the difference in pain intensity scores.

Acetaminophen, as discussed in previous sections, has a synergistic effect on the analgesia provided by hydrocodone. Acetaminophen, a nonopioid drug, is subject to ceiling effects, with a maximum effective single dose of at least 1000 mg. However, below this dose, the level of pain relief increases with increasing doses of acetaminophen. Thus, a 750-mg dose of acetaminophen in combination with a fixed opioid dose can be expected to provide more analgesia than a 650-mg or 660-mg dose of acetaminophen in combination with the same fixed opioid dose (Figure 7.2). Again, as illustrated in Figure 7.2, increasing the dose of acetaminophen from 500 to 1000 mg while keeping the oxycodone dose fixed at 5 mg also increases the level of analgesia.

Figure 7.2



Although **Maxidone™** offers high-dose acetaminophen, these doses are still within the recommended 4-gram daily limit for acetaminophen use. **Maxidone™** is an excellent analgesic choice for the relief of acute pain in patients who are otherwise healthy and who do not have risk factors for acetaminophen toxicity (eg, alcoholism, anorexia, hepatic or renal impairment). The adult dosage of **Maxidone™** is 1 tablet every 4 to 6 hours, as needed, up to a maximum of 5 tablets daily.

Strong Medicine for Strong Pain

Pain that is moderately severe requires strong analgesia. Although some patients may respond to lower doses of hydrocodone and acetaminophen, others will require more profound pain relief depending on the type of injury they have sustained and the severity of pain they are experiencing. When physicians treat pain aggressively with potent agents such as **Maxidone™**, their patients can expect to get back to their normal functioning sooner. Effective pain relief can mean fewer patients complaining of residual pain, fewer patients requiring dose increases, and fewer physician's office visits or phone calls.

Moderate to moderately severe pain usually occurs in an acute setting, such as the pain that occurs after a musculoskeletal injury. In the acute setting, adverse effects such as opioid dependence (with hydrocodone) and hepatotoxicity (with acetaminophen) are usually not a significant concern in otherwise healthy patients.

Although **Maxidone™** is a potent analgesic, it is not associated with the restrictions of the Schedule II opioids such as oxycodone (Percocet). Because hydrocodone in combination with acetaminophen has a Schedule III designation, **Maxidone™** can be conveniently prescribed over the telephone, making it potentially the strongest analgesic available without a triplicate prescription, and can be refilled up to 5 times over a 6-month period.

Competitive Products

Table 7.2 Zydone 7.5/400 • Vicodin ES • Lorcet Plus 7.5/650 • Anexsia 7.5/650 • Lortab 7.5/500 • Norco 7.5/325

Manufacturers:	Endo, Knoll, Forest, Mallinckrodt, UCB, Watson
Formulations:	7.5 mg hydrocodone/325–750 mg acetaminophen
Narcotic Control Schedule:	CIII
Indication:	Moderate to moderately severe pain

The Maxidone™ Advantage

- Contains 33% more hydrocodone than these formulations
- Can be expected to provide more analgesia than 7.5-mg hydrocodone formulations
- Contains more acetaminophen than all these formulations (except Vicodin ES)
- Can be expected to provide more analgesia than formulations containing <750 mg acetaminophen

Table 7.3 Zydone 10/400 • Lorcet 10/650 • Vicodin HP 10/660 • Anexsia 10/660 • Lortab 10/500 • Norco 10/325

Manufacturers:	Endo, Knoll, Forest, Mallinckrodt, UCB, Watson
Formulations:	10 mg hydrocodone/325–660 mg acetaminophen
Narcotic Control Schedule:	CIII
Indication:	Moderate to moderately severe pain

The Maxidone™ Advantage

- Contains more acetaminophen than all these formulations
- Can be expected to provide more analgesia than formulations containing <750 mg acetaminophen
- 30% less expensive than market leader Lorcet 10/650

Section 7 Summary

- **Maxidone™** contains the highest dose of hydrocodone and the highest dose of acetaminophen available in a single tablet.
- **Maxidone™** provides strong analgesia without the serious side effects associated with other strong opioid combinations (eg, oxycodone/acetaminophen).
- **Maxidone™** is potentially the strongest analgesic available without a triplicate prescription.
- The 750 mg of acetaminophen in each tablet is below the ceiling dose of 1000 mg for acetaminophen and thus provides more analgesia than lower doses of acetaminophen.
- At the maximum daily dose of 5 tablets, **Maxidone™** still remains within the 4-gram daily recommended limit for acetaminophen.
- The AHCPR guidelines recommend a starting dose of 10 mg hydrocodone in patients weighing >110 lbs for postoperative pain.

Frequently Asked Questions and Answers

Norco® For Physicians

Doctor

Why should I prescribe ***Norco®****?*

Representative

Only **Norco®** provides two unique formulations of hydrocodone and low-dose acetaminophen—5/325 and 7.5/325.

Doctor

I prefer to prescribe Vicodin 5/500 or Vicodin ES. Are these really different from ***Norco®****?*

Representative

Yes, both Vicodin formulations have more acetaminophen. In fact, Vicodin ES has 750 mg of acetaminophen, more than twice the amount in **Norco® 5/325** and **Norco® 7.5/325**. That's fine if you're interested in the analgesic action of acetaminophen. As you know, however, some types of pain are much more responsive to the CNS activity of hydrocodone. The large dose of acetaminophen may not only be unnecessary, but it may also limit the amount of hydrocodone that can be administered. Remember that Vicodin 5/500 has a daily dose limit of 8 tablets. There's also the problem of acetaminophen toxicity.

Doctor

What difference does a hundred or so milligrams of acetaminophen really make?

Representative

A hundred or so milligrams of acetaminophen in each tablet can add up to a big difference per day. Let me remind you, doctor, that the recommended daily limit of acetaminophen is 4 g for a person without any hepatic or renal impairment. So the acetaminophen in Vicodin ES limits the number of tablets patients can take to only 5 a day, and the number of Vicodin 5/500 tablets to 8 per day. And if the primary reason you're prescribing these combinations is for the effect of the hydrocodone, **Norco®** allows you to increase the hydrocodone dose without flirting with that 4-gram limit.

Even more important, many patients including the elderly, alcoholics, and those with low food intake or poor nutrition, should not be taking that full 4-gram daily dose. Acetaminophen toxicity can pose a real problem for these patients.

Remember, too, that your patients may be taking any one of the more than 100 OTC products that contain acetaminophen. This can increase their daily acetaminophen intake considerably and you may not even know about it.

Doctor

I don't think acetaminophen toxicity poses a problem for most of my patients.

Representative

Doctor, I'm sure you're aware of all the patients in your practice with overt hepatic dysfunction. But when you consider those who consume large amounts of alcohol, patients who are malnourished, and those on medications like barbiturates, phenothiazines, and warfarin, the number of patients who should limit acetaminophen intake begins to rise. Also, patients may not tell you that they're taking one of the more than 100 OTC products that contain acetaminophen. Most older patients have declining hepatic and renal function so smaller doses of acetaminophen might be prudent for this population as well. Why give more of something that's potentially harmful if it isn't necessary?

Doctor

Acetaminophen toxicity can't be that common.

Representative

Unfortunately, it's quite common. More than 64,000 incidents of accidental acetaminophen poisoning were reported in 1998, and most of these involved combination products. There have also been anecdotal reports of liver failure in patients who have taken Vicodin concomitantly with other acetaminophen-containing OTC products. So you see, Doctor, the possibility of acetaminophen toxicity is very real in these situations.

Doctor

I often prescribe Percocet when I need a more potent analgesic—it doesn't contain any more acetaminophen than ***Norco®****.*

Representative

The hydrocodone in **Norco®** formulations is a Schedule III substance, not a Schedule II like the oxycodone in Percocet, even though both opioids are indicated for moderate to moderately severe pain. It certainly simplifies prescribing—you can avoid filling out a prescription in triplicate and you can even phone in a prescription in most states.

Doctor

I can avoid the acetaminophen problem altogether and prescribe Vicoprofen.

Representative

But remember Doctor, the ibuprofen in Vicoprofen has the GI and bleeding side effects that are associated with all the NSAIDs. Certainly, this would not be a good choice in the postoperative setting.

Doctor

If I don't want to prescribe a Schedule II, I can use Tylenol #4 with codeine. That only has 300 mg of acetaminophen.

Representative

Tylenol #4 has 60 mg of codeine; that's quite a lot. Many patients have trouble tolerating that much codeine at once and may experience increasing constipation.

Doctor

Am I going to get complaints from my patients about the price of ***Norco® 5/325*** *or* ***Norco® 7.5/325?***

Representative

No. Both **Norco® 5/325** and **Norco® 7.5/325** have been priced competitively against combinations with similar amounts of hydrocodone. And with its small size, the tablet should be easier for patients to take, both physically and financially.

Norco® For Trade Customers

Customer

Why should I stock two more hydrocodone/APAP combinations?

Representative

Because **Norco® 5/325** and **Norco® 7.5/325** are unique formulations. No other brand combines the most frequently prescribed doses of hydrocodone with lower-dose acetaminophen, and you will not be able to directly substitute any other product for either **Norco®** prescription.

Plus **Norco®** is competitively priced at an AWP of $65.00 per 100 tablets for the 5/325 formulation and $74.60 for the 7.5/325 formulation.

Customer

Why low-dose acetaminophen? What can be safer than Tylenol?

Representative

Unfortunately, acetaminophen is not as benign a drug as we have traditionally believed. The recommended daily limit for acetaminophen is 4 g, and even that dose causes liver toxicity in some patients in the long term. On the other hand, hydrocodone can be dosed up to 120 or 200 mg or even more daily. So if acetaminophen levels are too high, combination products can come up short on hydrocodone.

Plus doctors and other prescribers are becoming sensitive to the problem of acetaminophen toxicity. More than 64,000 incidents of accidental acetaminophen poisoning were reported in 1998, and most of these involved combination products.

Sometimes, patients don't realize that even acetaminophen, when taken in excess, can be very dangerous. Some patients taking hydrocodone/APAP combinations for pain may also take cough, cold, or allergy medications that contain APAP, unaware that they are exceeding the recommended daily 4-gram limit. With **Norco®**, there is less chance that patients who self-medicate with acetaminophen will exceed the 4-gram limit and increase their risk of liver toxicity.

Customer

There is a lot of competition. Am I going to move this stock?

Representative

Absolutely. **Norco®** has a high-powered promotional campaign underway to ensure that the product message gets out. Plus, the promotion is being directed specifically at high prescribers of these products, where the message can have the greatest impact on prescriptions.

Maxidone™ For Physicians

Doctor

*Why should I prescribe **Maxidone**™?*

Representative

Maxidone™ is the most potent hydrocodone/acetaminophen product available on the market. **Maxidone**™ is an excellent choice for patients whose pain would not be expected to be relieved with lower doses of hydrocodone/acetaminophen.

Doctor

Do patients really need that much hydrocodone? I prefer to prescribe the 5-mg or 7.5-mg formulations.

Representative

So do most physicians. But the AHCPR guidelines recommend an initial dose of 10 mg hydrocodone in patients weighing more than 110 pounds. Moreover, some patients and some types of pain just don't respond to the lower doses of hydrocodone. And as you know, 10 mg hydrocodone will provide more analgesia than 5 mg or 7.5 mg.

Doctor

*I could prescribe Vicodin HP 10/660. Is **Maxidone**™ really different?*

Representative

Yes. **Maxidone**™ contains 90 mg more acetaminophen per tablet. And as you know doctor, below the ceiling dose, any extra acetaminophen is going to help provide more pain relief.

Doctor

Sometimes I prescribe Percocet or Percodan when I need a strong analgesic.

Representative

Doctor, since it is a Class III opioid, **Maxidone™** is possibly the most potent analgesic you can give your patients without having to fill out a prescription in triplicate. You can even prescribe it over the phone and get prescriptions refilled up to 5 times over a 6-month period.

Doctor

*With such a high dose of acetaminophen per tablet, isn't there a risk for hepatotoxicity with **Maxidone™**?*

Representative

Doctor, even though **Maxidone™** contains 750 mg per tablet, the daily dose is still within the 4-gram limit for acetaminophen use. Moreover, in the acute setting in otherwise healthy patients, acetaminophen toxicity is usually not a concern.

Doctor

*Are my patients going to complain about the price of **Maxidone™**?*

Representative

Doctor, **Maxidone™**'s price is comparable to that of the other 10-mg hydrocodone products.

Maxidone™ for Trade Customers

Customer

*Why should I stock **Maxidone™**?*

Representative

You know that hydrocodone/acetaminophen combinations are the number 1 prescribed products in terms of dollar sales. **Maxidone™** is a potent analgesic in this drug class.

Customer

I stock so many hydrocodone/acetaminophen combinations. Why stock yet another one?

Representative

Because **Maxidone™** is a unique formulation that provides the highest dose of hydrocodone and highest dose of acetaminophen available in a single tablet. In fact, it's possibly the most potent analgesic available without a triplicate prescription. That means less paperwork for you.

Customer

Am I going to move this stock?

Representative

Most certainly. Doctors prescribe the high-dose acetaminophen combinations 15 times more often than they do lower-dose combinations. So you're likely to fill a lot of prescriptions for **Maxidone™**. Plus, it's a unique formulation so you won't be able to substitute it with a generic.

Moreover, Watson's commitment to **Maxidone™** in terms of sales and marketing efforts is the same as it was for **Norco®**, which was the number 1 selling branded hydrocodone product last year.

Customer

*What do I need to tell my customers about **Maxidone™**?*

Representative

Remember that **Maxidone™** is a strong analgesic that is meant to relieve moderate to moderately severe pain usually in the acute setting. It contains a high dose of acetaminophen so your customers need to be careful that they do not take OTC medications that contain acetaminophen and inadvertently exceed the daily recommended 4-gram limit.

Customer

*Is **Maxidone™** competitively priced?*

Representative

Yes. In fact it is less expensive than Lorcet 10/650 even though it contains more acetaminophen.

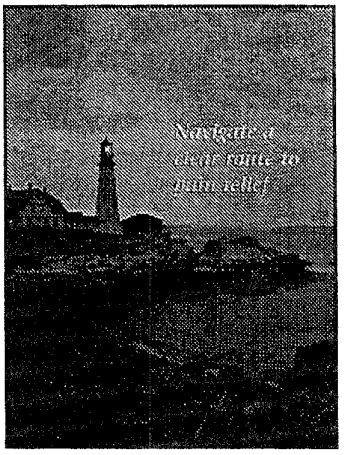
Sample Details

Norco® Sample Detail

This 8-page visual aid will serve as your primary selling tool. The front cover provides a teaser to the first spread—an overview of the current medical perspective on acetaminophen—setting the stage for a **Norco®** detail. The second and third spreads are a comprehensive description of the key selling points for **Norco® 5/325** and **Norco® 7.5/325**, respectively. Discussing the first spread in addition to at least one of the **Norco®** spreads will prove most effective in situations when time allows for a complete presentation. The back cover offers a summary of benefits for a full detail, and may also be used as an overview in a reminder detail. Please remember that this piece is not a leave behind, and a file card should be left with the physician to fulfill the requirements of full prescribing information.

The message remains compelling for both products: **Norco®** allows a clear route to pain relief, providing an appropriate level of hydrocodone along with a rational dose of acetaminophen. The hydrocodone/acetaminophen combination provides excellent pain relief, but even at the maximum recommended daily dose, it does not exceed the 4-gram daily limit for acetaminophen use recommended by the United States Pharmacopoeial Drug Index (USP DI).

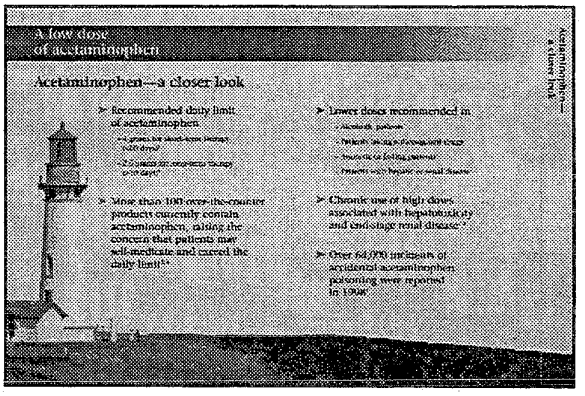
"Doctor, just like a lighthouse helps ships navigate around rocks, reefs, and shallow water, you want to help your patients by providing them with effective pain relief without the concerns that may be inherent when you prescribe high doses of acetaminophen."



Front Cover Background Information

The scene is a lighthouse at night. The fact that it is night is suggestive of concern, as ship captains will lose the use of their eyes to navigate the tricky waters that inevitably invite the placement of a lighthouse. Like each strength

of **Norco®**, each lighthouse beacon (and markings) is unique, and gives ship captains an immediate point of reference by which to steer. In drawing the analogy to pain therapy, you're suggesting to the physician that, like navigating the waters surrounding a lighthouse, prescribing a product for pain relief can result in a successful voyage.



"Doctor, if we take a closer look at acetaminophen, we see that the recommended daily limit is just 4 grams for short-term use—10 days or less, and 2.6 grams for a longer duration of therapy. All hydrocodone/acetaminophen products stay below the 4-gram level within the recommended maximum daily prescribing limits. So if you prescribe any of these preparations for less than 10 days, there is less concern."

"However, you can't always be sure that these products are taken in a vacuum. More than 100 OTC products contain acetaminophen, including many cough, cold, and allergy preparations. Acetaminophen is not an obvious ingredient in many of these OTC products, suggesting that patients would have to read the ingredient list of any products that they are taking while on the opioid. And how many of your patients would be so diligent?"

"In addition, some groups of patients can tolerate even less acetaminophen than the norm, including alcoholics, those taking anticoagulants, anorexic or fasting patients, or those with preexisting hepatic or renal disease."

"The ramifications of using too much acetaminophen on a regular basis can be severe, and such use has been associated with both liver and kidney disease."

"Finally, it is important to realize that acetaminophen toxicity is not a rare occurrence. The American Association of Poison Control

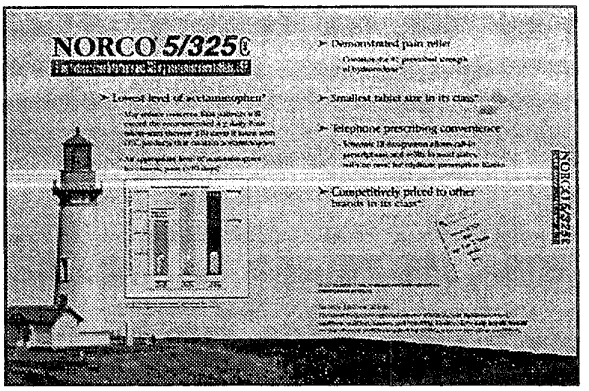
Centers identified more than 64,000 incidents of accidental acetaminophen poisoning."

"Overall, then, I think you can see how a lower dose of acetaminophen might be preferable to a higher dose in treating patients with moderate to moderately severe pain."

First Spread Background Information

As the graphic illustrates, it is now daytime at the lighthouse, and the concerns of a nighttime voyage have passed. You have now given the physician the medical rationale to avoid the adverse effects caused by regular use of excessive doses of acetaminophen—a concern both in higher-dose acetaminophen and hydrocodone formulations, and in common OTC products that patients may take simultaneously with their pain medication.

Low-dose acetaminophen use is the core concept behind the entire **Norco®** product line. The belief that acetaminophen is a harmless analgesic that can be taken at will has been difficult to dispel among physicians. Since **Norco®** contains acetaminophen, we walk a fine line between acknowledging the efficacy of the drug, and disparaging its toxicity. Therefore, the message that must be translated to prescribers is that acetaminophen is an effective analgesic that potentiates the pain-relieving effects of hydrocodone, but should be taken at specific dose levels in order to avoid long-term toxicities.



"Doctor, that's why Norco® 5/325 is an excellent choice for so many patients. With the lowest therapeutic level of acetaminophen of all of the hydrocodone preparations, Norco® 5/325 may reduce the concern that patients will exceed the 4-gram daily limit for short-term therapy if taken with OTC products containing acetaminophen."

"Furthermore, as this graph illustrates, Norco® 5/325 contains an appropriate level of acetaminophen for long-term use, greater than 10 days. In fact, you could give up to 12 Norco® 5/325 tablets per day and remain under the 4-gram daily limit for acetaminophen."

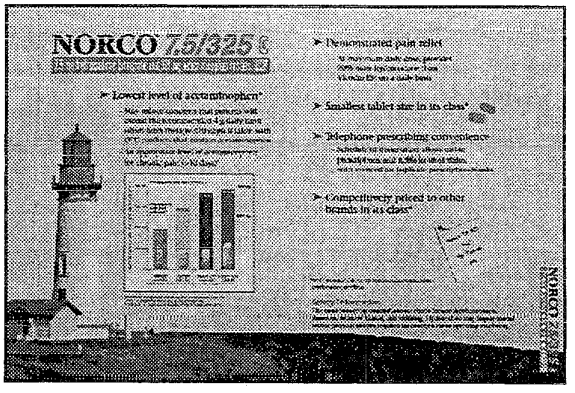
"With 5 mg of hydrocodone per tablet, Norco® 5/325 contains the most often prescribed strength of hydrocodone, and in the smallest tablet size of its class."

"In addition, as a Schedule III drug, Norco® 5/325 provides telephone prescribing convenience, with no need for triplicate prescription blanks."

"Finally, Norco® 5/325 is competitively priced to other branded hydrocodone preparations, a factor that your patients are sure to appreciate. The prescription can be simply written as shown: Norco 5 slash 325, number 80, and you may prescribe one or two tablets every 4-6 hours as needed."

Second Spread Background Information

This is the key page for the detail of **Norco® 5/325**, as it clearly explains the reasons to prescribe the formulation. These points should be completely covered whenever possible to target physicians, highlighting both the safety and efficacy of the formulation.



"And, Doctor, for your patients who require more hydrocodone with the same low dose of acetaminophen, Norco® 7.5/325 is an excellent choice. Norco® 7.5/325 has the lowest therapeutic level of acetaminophen of all of the 7.5-mg hydrocodone/acetaminophen preparations, reducing the concern that patients will exceed the 4-gram daily limit for short-term therapy if taken with OTC products containing acetaminophen."

"Like Norco® 5/325, Norco® 7.5/325 contains an appropriate level of acetaminophen for long-term use."

"With 7.5 mg of hydrocodone per tablet, Norco® 7.5/325 provides 20% more hydrocodone than Vicodin ES on a daily basis at maximum dose. And it does so with the smallest tablet size of its class."

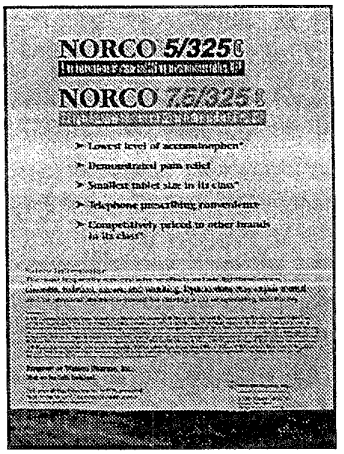
"In addition, as a Schedule III drug, Norco® 7.5/325 provides the convenience of telephone prescribing and no need for triplicate blanks."

"Finally, Norco® 7.5/325 is competitively priced to other branded hydrocodone preparations, a factor that your patients are sure to appreciate. The prescription can be simply written as shown: Norco 7 point 5 slash 325, number 60, one tablet every 4-6 hours as needed."

Third Spread Background Information

This script is to be used if you are detailing both strengths of **Norco®**. It should be modified to resemble the second spread detail if the physician is a 7.5/325 target only. These points should be completely covered whenever possible to target physicians, highlighting both the safety and efficacy of the formulation.

"With their low level of acetaminophen, demonstrated efficacy, and small tablet size, these two Norco® formulations are excellent choices for your patients with moderate to moderately severe pain. In addition, their telephone prescribing convenience and competitive pricing measure up well with other formulations in their class."



"Doctor, can I count on you to prescribe Norco® 5/325 and Norco® 7.5/325 for your patients with moderate to moderately severe pain?"

"Doctor, I would like to remind you to specify the appropriate dose when prescribing Norco®. Since Norco® is now available in multiple strengths, the pharmacist may be confused if a dose is not specified."

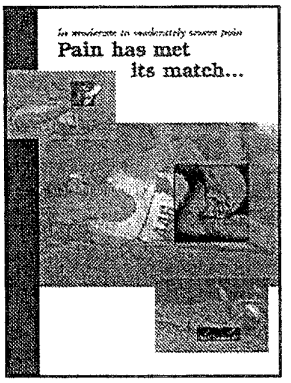
"Would you like samples of Norco® 5/325 to start your patients on therapy?"

"Thank you for your time, and your commitment to prescribe Norco®. Please call me if I can be of any further assistance."

Maxidone™ Sample Detail

The 4-page visual aid will serve as your primary selling tool. The front cover provides an effective lead-in to the **Maxidone™** detail. The inside spread provides a comprehensive description of the key selling points in situations when you can give a complete presentation. The back cover offers a summary of benefits for a full detail, and may also be used as an overview in a reminder detail. Please remember that this piece is not a leave behind, and a file card should be left with the physician to fulfill the requirements of full prescribing information.

"Doctor, I'm sure you see your share of injuries as a result of sporting activities by weekend warriors or the Mr. Fix-it that needs a little fixing himself. Now, when your patients present with moderate to moderately severe pain, their pain has met its match..."

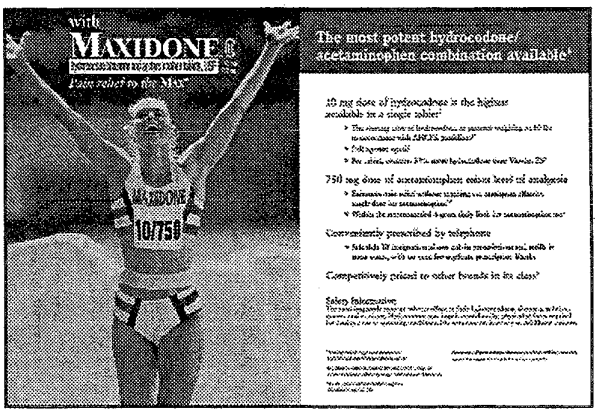


Front Cover Background Information

The copy, in combination with the scenarios represented, immediately identifies a patient profile for your physician. The copy indicates that you are offering a solution for the physician to treat patients with moderate to moderately severe pain.

The photographs used on the cover highlight some of the most common causes of pain that result in prescriptions for combination opioid analgesics. According to Physician Drug & Diagnosis Audit, musculoskeletal injuries account for 78% of the top 25 diagnoses for which physicians are prescribing hydrocodone/acetaminophen. The American Academy of Orthopaedic Surgeons (AAOS) reports that there are 33 million trauma- and sports-related musculoskeletal injuries each year. More than 90% of these injuries require medical attention and result in 85 million days of lost productivity (work/school) estimated to cost more than $26 billion. Your target physicians will immediately identify with these patients, which will set the stage for you to deliver an effective **Maxidone™** message.

"with Maxidone™. Maxidone™ delivers pain relief to the max..."

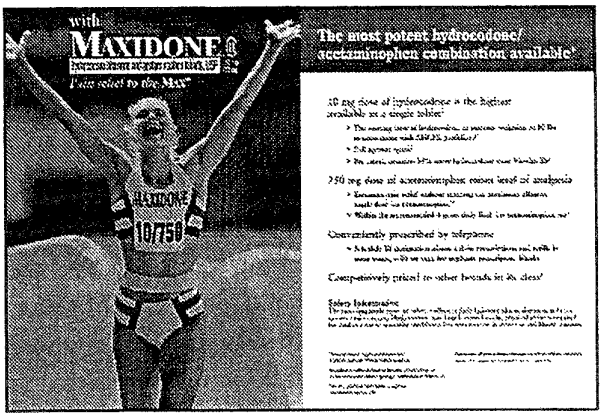


Page Two Background Information

The photograph immediately illustrates the solution to the problem identified on the cover. The most prominent image on the cover—the runner in pain—is shown back in action. The copy supports that **Maxidone™** helps get patients back on their feet.

Again, the AAOS indicates that musculoskeletal injuries are usually painful and at least temporarily debilitating. These injuries require that patients reduce activities (sports, etc.) for an average of 7.6 days, for a total of 250 million days each year. Primary goals of the physician include reducing the patient's level of pain and getting them back to their normal routine as soon as possible.

"...by offering the most potent hydrocodone/ acetaminophen combination available."



"Doctor, the 10-mg dose of hydrocodone is the highest available in a single tablet, and is the appropriate starting dose in patients weighing greater than 110 pounds, according to the Agency for Health Care Policy and Research. Maxidone™ is a full agonist opioid and contains 33% more hydrocodone per tablet than Vicodin ES."

"Maxidone™ raises the level of analgesia by delivering the most potent dose of acetaminophen available. The 750-mg dose of acetaminophen enhances the pain relief of hydrocodone without reaching the ceiling dose, the maximum effective single dose for acetaminophen. The level of acetaminophen at the maximum daily dose of Maxidone™ is within the recommended 4-gram daily limit for acetaminophen."

"Doctor, you can prescribe Maxidone™ conveniently by telephone. Its schedule III designation allows call-in prescriptions and up to 5 refills over a 6-month period in most states, with no need for triplicate prescription blanks."

"And doctor, in addition to effective pain relief, your patients will appreciate that Maxidone™ is competitively priced to other branded 10-mg hydrocodone products."

Page Three Background Information

This page is the most important page for physicians, as it explicitly details the reasons that they should prescribe **Maxidone™**. These points should be covered whenever possible to target physicians. Physicians will recognize that

Maxidone™ offers their patients effective pain relief, as it is the most potent hydrocodone/acetaminophen combination available. The AHCPR reference offers expert opinion to support the physician's decision to prescribe a 10-mg dose of hydrocodone. Prescriptions for 10-mg hydrocodone products are increasing at a 22% annual rate.

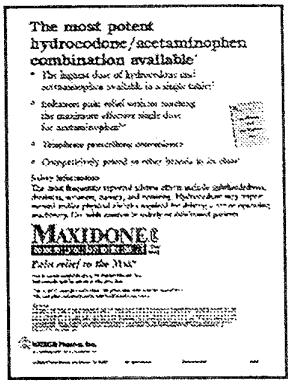
Opioids are classified according to their effects on pain receptors, such as mu (pronounced "myo͞o"), delta, and kappa receptors. Of the three classes of opioids (full agonist, partial agonist, and mixed agonist-antagonists), many physicians prefer a full agonist opioid. Hydrocodone is a full agonist opioid. Full agonist opioids bind tightly to pain receptors. Their effectiveness with increasing doses is not limited by a ceiling effect. Partial agonists bind to pain receptors, but produce less than complete effects, even when bound to all receptors. Mixed opioids are antagonists to some receptors; that is, they bind to the pain receptors, but do not produce any effect. To other receptors they do have an agonist effect.

Vicodin ES, one of the original "high-dose" combination opioids, remains a widely prescribed product. **Maxidone™** offers the same adjunctive relief that a 750-mg dose of acetaminophen provides, with 33% more hydrocodone. Remember that hydrocodone is not limited by a ceiling effect, so a higher dose will result in additional pain relief.

Acetaminophen is recognized to have a synergistic effect on the analgesia of hydrocodone. The acetaminophen level in **Maxidone™** provides more relief than lower doses of acetaminophen because it is below the ceiling dose, the maximum effective single dose for acetaminophen (which is at least 1 gram). So a 750-mg dose of acetaminophen provides more relief than a 650- or a 660-mg dose. Please keep in mind that clinical trials do not exist to support comparative claims for **Maxidone™** against these products.

The ceiling effect should not be confused with the 4-gram daily limit of acetaminophen for short-term use, or the 2.6-gram daily limit for long-term use that is generally recognized by experts.

Physicians should always be reminded that **Maxidone™** is a Schedule III product, as it offers conveniences that Percocet and other C-II drugs do not. Also, focus groups with high-prescribing physicians support that they are cost-conscious, and want to be assured that a product is competitively priced to other brands.



"Doctor, when your patients present with pain, Maxidone™ delivers pain relief to the Max. Remember that Maxidone™..."

- *"Is the most potent hydrocodone/ acetaminophen combination available*
- *Enhances pain relief without reaching the ceiling dose for acetaminophen*
- *Can be conveniently prescribed by telephone*
- *And is competitively priced to other brands in its class"*

"Doctor, Maxidone™ is an excellent choice for your patients in pain. The prescription can simply be written as Maxidone, number 50, one tab every 4 to 6 hours, as needed. Will you prescribe Maxidone™ when your patients present with moderate to moderately severe pain?"

"Doctor, thank you for your commitment to prescribe Maxidone™. Would you like some patient starter samples?"

Quiz

1. Which is not characteristic of chronic pain?

A. It lasts more than 3 months

B. It has a sudden onset

C. It does not respond immediately to treatment

D. The affected area is large or inconstant

2. The body's own naturally occurring analgesics are called:

A. Opiates

B. Serotonin inhibitors

C. Endorphins

D. Opioids

3. Which of the following is not involved in the inflammation cascade?

A. Prostaglandins

B. Leukotrienes

C. Arachidonic acid

D. Dynorphin

4. Which of the following is more active against COX-2 than COX-1?

A. Acetaminophen

B. Aspirin

C. Piroxicam

D. Rofecoxib

5. The gastrointestinal adverse effects of the NSAIDs and aspirin are mainly due to their:

A. Blockade of prostaglandin synthesis

B. Effects on stomach pH

C. Inhibition of COX-1

D. Inhibition of arachidonic acid production

6. Acetaminophen produces its analgesic effect mainly by:

A. Blocking prostaglandin synthesis at peripheral sites

B. Blocking prostaglandin synthesis in the CNS

C. Reducing inflammation

D. Altering the brain's perception of pain

7. All of the following bind to the opioid receptor except:

A. Tramadol

B. Morphine

C. Meperidine

D. Indomethacin

8. Which is not true of opioid/nonopioid analgesic combinations?

A. They provide higher levels of analgesia than either component alone.

B. They allow for greater analgesia without escalating the opioid dose.

C. They are the first-line agents for management of mild pain.

D. They are recommended for moderate to severe pain.

9. Pain medication should generally be administered:

A. As needed

B. Around the clock

C. Every 4 to 6 hours

D. In accordance with the caregiver's wishes

10. Tolerance to the analgesic effects of opioids is usually managed by:

A. Reducing the dose

B. Changing to another opioid

C. Discontinuing treatment for a few hours

D. Escalating the dose

11. Match the following products with the appropriate hydrocodone/acetaminophen dose.

Lorcet Plus	5/500
Zydone	7.5/750
Vicodin	7.5/650
Vicodin ES	10/400
Lortab	7.5/500

12. The maximum recommended daily limit of acetaminophen for short-term use is:

A. 1000 mg

B. 4.0 g

C. 2.6 g

D. 500 mg

13. Hydrocodone has an:

A. Onset of action of 30 to 45 minutes and a duration of analgesia of 2 to 4 hours

B. Onset of action of 30 to 45 minutes and a duration of analgesia of 4 to 6 hours

C. Onset of action of 10 to 30 minutes and a duration of analgesia of 2 to 4 hours

D. Onset of action of 10 to 30 minutes and a duration of analgesia of 4 to 6 hours

14. Which is not a common side effect of opioid analgesics?

A. Constipation

B. Respiratory depression

C. Cough

D. Sedation

15. Hydrocodone is similar to morphine in its:

A. Abuse potential

B. Onset of analgesic effect

C. Incidence of constipation

D. Tendency to induce respiratory depression

16. In the hydrocodone/acetaminophen market, the majority of prescriptions are written for the:

A. 5 mg hydrocodone dose

B. 10 mg hydrocodone dose

C. 7.5 mg hydrocodone dose

D. B and C

17. Which of the following acetaminophen doses would be expected to provide equivalent levels of analgesia?

A. 500 mg and 1000 mg

B. 660 mg and 750 mg

C. 500 mg and 750 mg

D. 1000 mg and 1200 mg

18. Which of the following is not a risk factor for acetaminophen toxicity?

A. Alcoholism

B. Obesity

C. Anorexia

D. Liver impairment

19. List at least 2 advantages of ***Norco®*** *over Vicoprofen.*

_____

_____

20. The daily limit for ***Maxidone™ (10/750)*** *is:*

A. 8 tablets

B. 5 tablets

C. 6 tablets

D. 12 tablets

Glossary of Terms

Acetaminophen—a non-narcotic analgesic and antipyretic.

Addiction—defined by some authorities as a state of physical dependence characterized by tolerance and withdrawal, and by other authorities to include psychological dependence.

Adjuvant drug—a drug that aids another.

Agonist—a drug that combines with the appropriate receptors to cause a response; the opposite of an antagonist, which is a drug that blocks a response.

Alkaloid—any one of hundreds of basic (the opposite of acidic) substances produced by plants, often used for medicinal purposes.

Amphetamines—a family of drugs that have a stimulating effect on both the central and peripheral nervous systems. Their abuse may lead to psychological or physical dependence, or both.

Analgesia—absence of sensibility to pain; in particular, the relief of pain without loss of consciousness.

Analgesic—an agent that alleviates pain without causing loss of consciousness.

Antiemetic—an agent that stops or prevents vomiting.

Antihistamine—a drug that interferes with the production of histamine. Histamine mediates the classic allergic symptoms of runny nose; itchy, watery eyes; and so on.

Antipyretic—a drug that reduces fever.

Arachidonic acid—a substance that is a precursor of prostaglandins, as well as a building block of substances that are involved in allergic responses, vasoconstriction, and increased vascular permeability.

Aspirin—a non-narcotic salicylate analgesic.

Autonomic—referring to the involuntary part of the nervous system, which governs basic functions such as breathing, heartbeat, and dilation of the pupils.

Barbiturates—a class of sedative-hypnotic and antiseizure drugs. Some have a high potential for abuse.

Beta-endorphin—one of the most commonly occurring POMC peptides.

Bradykinin—a peptide produced by activation of the kinin system (which regulates blood vessel dilation) by inflammatory conditions.

CNS—central nervous system; the brain and spinal cord.

Congener—something closely related to another, such as two chemical compounds.

Constipation—infrequent or incomplete bowel movements.

Cyclooxygenase—enzyme converting arachidonic acid into prostaglandins.

Dependence, physical—the use of a drug to prevent withdrawal symptoms.

Dependence, psychological or emotional—the use of a drug to relieve emotional discomfort or tension.

Diaphoresis—perspiration, especially profuse perspiration.

Dynorphin—one of three naturally occurring neuropeptides (the endorphins) that bind to the opioid receptors in the brain and exhibit analgesic activity.

Dysphoria—discomfort.

Endorphins—opioid peptides which bind to opiate receptors in the brain; some exhibit potent analgesic activity.

Enkephalins—pentapeptides that function as neurotransmitters or neuromodulators at many locations in the brain and spinal cord. They have a role in pain perception, as well as mood, movement, and neuroendocrine regulation.

Enzyme—a protein that catalyzes chemical reactions in other substances without being altered or destroyed by those reactions.

Equilibrium—a state of balance.

Etiologic—referring to the cause and development of a disease.

GI—gastrointestinal.

Histamine—a product of amino acids that stimulates gastric secretion, constricts bronchial muscles, and dilatcs blood vessels.

Hyperalgesia—extreme sensitivity to painful stimulation.

Hypertension—high blood pressure.

Hypothalamus—part of the forebrain; involved in the function of the autonomic nervous system.

Inflammation—a protective response to injured tissue, characterized by any or all of these factors: pain, heat, redness, swelling, and loss of function.

Ischemia—a deficiency of blood in part of the body due to constriction or obstruction of a blood vessel.

Leukotriene—one of a group of compounds formed from arachidonic acid that function as regulators of allergic and inflammatory reactions.

Lipoxygenase (5-lipoxygenase)—an enzyme involved in the oxidation of polyunsaturated fatty acids to form hydroperoxides.

Macrophage—large, amoeba-like cell that ingests bacteria and foreign particles.

Malignancies—cancer; areas of severe abnormality that resist treatment and tend to grow worse.

Mesencephalon—the midbrain.

Morphine—an analgesic produced from opium that provides sedation and relieves anxiety.

Narcotic—a substance that produces insensibility or stupor, such as any drug that has opium-like properties.

Neurocranium—the part of the skull that encloses the brain.

Neurotransmitter—substance released from a presynaptic neuron of the central or peripheral nervous system that travels across the synapse to excite a target cell.

Non-narcotic—does not bind to opiate receptors.

NSAID—nonsteroidal anti-inflammatory drug.

Opiate—a remedy containing or derived from opium.

Opioid—a synthetic narcotic that has opiate-like effects but is not derived from opium.

Opioid receptors—receptor sites in the brain to which narcotics bind to produce analgesic effects upon the central nervous system.

Opium—milky fluid from the unripe seed pods of the poppy plant, used to ease pain, dysphoria, diarrhea, spasms, and insomnia.

Pain—an unpleasant sensation resulting from the stimulation of specialized nerve endings.

Pain, acute—the presence of severe discomfort of a relatively short duration. It usually is characterized by a sudden onset and subsides with treatment.

Pain, chronic—pain that continues over an extended period of time.

Peptide—a chain of amino acids.

Periosteum—a thick membrane covering the surface of a bone.

Peripheral—at the outer region of an organ or system.

Phospholipid—a lipid (fatty substance) that contains phosphate, a major form of lipid in all cell membranes.

Physiologic—related to normal physical functions.

Pons—a connective slip of tissue between two parts of an organ. In the central nervous system, it is the part of the brain lying between the medulla oblongata and the mesencephalon.

Prostaglandins—any of a group of compounds that are extremely potent mediators of a diverse group of physiologic processes.

Protein—any of a group of complex organic compounds which contain carbon, hydrogen, oxygen, and nitrogen.

Proteolytic—that which splits proteins, especially enzymes.

Psychic—related to the mind.

Reticular—part of the central and peripheral nervous system that does not make up the nerves.

Sedation—a state of calmness, especially when induced by medication.

Sensorium—a term often used to refer to a person's consciousness or mental clarity.

Serotonin—a chemical compound that, among many things, serves as a central neurotransmitter.

Somatic—structures of the body associated with the body wall, such as the skeletal musculature, rather than those associated with the internal organs.

Tachycardia—excessively rapid heartbeat; the term is usually applied when the heart rate is above 100 beats per minute.

Tactile—relating to the sense of touch.

Thalamus—part of the forebrain; helps control senses, behavior, and language.

Tolerance—the ability to endure unusually large doses of a drug.

Tolerance, acquired—a decreasing response to repeated, constant doses of a drug.

Turturro MA, Paris PM. Oral narcotic analgesics. Choosing the most appropriate agent for acute pain. *Postgrad Med.* 1991;90:89–90,93–95.

Oral narcotic (opioid) analgesics are effective for the short-term management of acute pain due to migraine and other headache syndromes, back pain, renal colic, and soft tissue trauma. Side effects associated with opioid use are usually mild and predictable, and include gastrointestinal (GI) disturbances, sedation, and euphoria; however, excessive doses can lead to respiratory depression. Short-term use of opioid analgesics rarely results in addiction in patients with no previous history of addiction.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and other nonnarcotic analgesics are effective for mild to moderate pain and are generally safe. However, opioids may be preferred for patients at risk of such NSAIDs-related complications as GI bleeding and renal failure. Opioids and NSAIDs act synergistically to produce a greater analgesic effect than a higher dose of either agent alone, such that most opioids are marketed in combination with an NSAID or other nonnarcotic analgesic.

There are important pharmacologic differences among opioid analgesics. Codeine has a limited analgesic potency and low addiction potential, but produces a relatively high degree of sedation and a high incidence of GI side effects. Hydrocodone is more potent but less sedating and less constipating, and may be more effective. Hydromorphone and oxycodone have limited roles in acute pain management, since they produce significant euphoria and consequently carry a potential for abuse. Propoxyphene produces marked sedation, and overdose may cause refractory seizures or respiratory depression. Pentazocine, an opioid agonist-antagonist, has a ceiling effect for respiratory depression but can lead to withdrawal in patients addicted to pure opioid agonists. It also produces psychomimetic reactions and may be abused in combination with the antihistamine tripelennamine hydrochloride.

Other opioids usually administered parenterally may be used orally for pain. Relatively high oral doses of morphine and meperidine are required for adequate pain relief. Both meperidine and methadone have relatively short durations of action, and accumulation after repeated doses can lead to seizures, sedation, and CNS depression.

Opioid (narcotic) analgesics (systemic). In: *USP-DI* Drug Information for the Health Care Professional, 15th edition. Volume I. Englewood, CO: Micromedex, Inc. 1995, pp2084–2085.

Pharmacokinetic studies have demonstrated that hydrocodone* has a somewhat longer half-life than oxycodone† (3.8 hours vs 2-3 hours). Both agents are eliminated entirely through renal mechanisms.

The onset of analgesic action of hydrocodone occurs 10 to 30 minutes after oral administration, reaching a peak effect 30 to 60 minutes after ingestion. The duration of hydrocodone's analgesic and antitussive effects is 4 to 6 hours. The analgesic effect of oxycodone peaks at 60 minutes after oral administration and has a slightly shorter duration of 3 to 4 hours.

As with all opioids, the first sign of tolerance is usually a decrease in the duration of an adequate analgesic effect. The duration of effect may be longer in geriatric patients due to a decreased rate of clearance.

*Classified as a Schedule III drug by the U.S. Controlled Substances Act.
†Classified as a schedule II drug by the U.S. Controlled Substances Act.

Schiødt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. *N Engl J Med*. 1997;337:1112–1117.

Hepatotoxicity following acetaminophen overdose has been described in two distinct clinical syndromes. Acute liver failure in individuals who attempt suicide by acetaminophen ingestion is often associated with multiorgan failure, nephrotoxicity, and occasionally pancreatitis. Hepatotoxicity can also occur in alcoholics or fasting individuals who ingest small amounts of acetaminophen for pain relief, and alcohol use or starvation appears to worsen the liver injury. In a recent study of patients hospitalized for acetaminophen overdose, nearly twice as much acetaminophen had been ingested during suicide attempts than with accidental overdose; however, accidental overdose was associated with low or undetectable blood levels of acetaminophen, higher rates of morbidity (severe liver necrosis, hepatic coma, acute liver failure) and mortality (19% vs 2%). Accidental overdose was also associated with a higher rate of chronic alcohol use.

The reasons given for overdosing in the accidental-overdose group included too-frequent dosing (such as every 2 hours) or overdosing with >1 g per dose due to persistent pain. Also, patients reported ingesting compounds they didn't know contained acetaminophen, or simultaneously ingested multiple preparations of acetaminophen. Some claimed ignorance of toxic effects in general or of the dosing limit, and others had a clouded sensorium due to alcohol.

Several factors may explain the less favorable clinical outcomes among the patients with accidental acetaminophen overdose. They were likely to present longer after ingestion (>24 to 48 hours), when blood levels could be expected to be low and when the effect of an antidote (acetylcysteine) would be less than maximal. In addition, it is possible that patients with subclinical liver damage may not have reported to the hospital at all, which could account for the more severe forms of liver injury among the patients with accidental overdose. Conversely, the patients who attempted suicide were more likely to present to the hospital earlier, when the prompt use of acetylcysteine would reduce both the incidence and severity of toxic effects.

In this study, accidental misuse of acetaminophen with doses only slightly above, or even within, the therapeutic range was associated with severe hepatotoxicity characterized by high levels of aminotransferase. These observations appear to implicate alcohol and fasting as contributing factors and distinguish this form of liver injury from alcoholic hepatitis, alcoholic cirrhosis, most forms of viral hepatitis, and other forms of acute liver injury.

Hench PK, Weart CW, Whitcomb DC. Acetaminophen toxicity. When to worry, what to do. *Patient Care.* 1996;January:3–11.

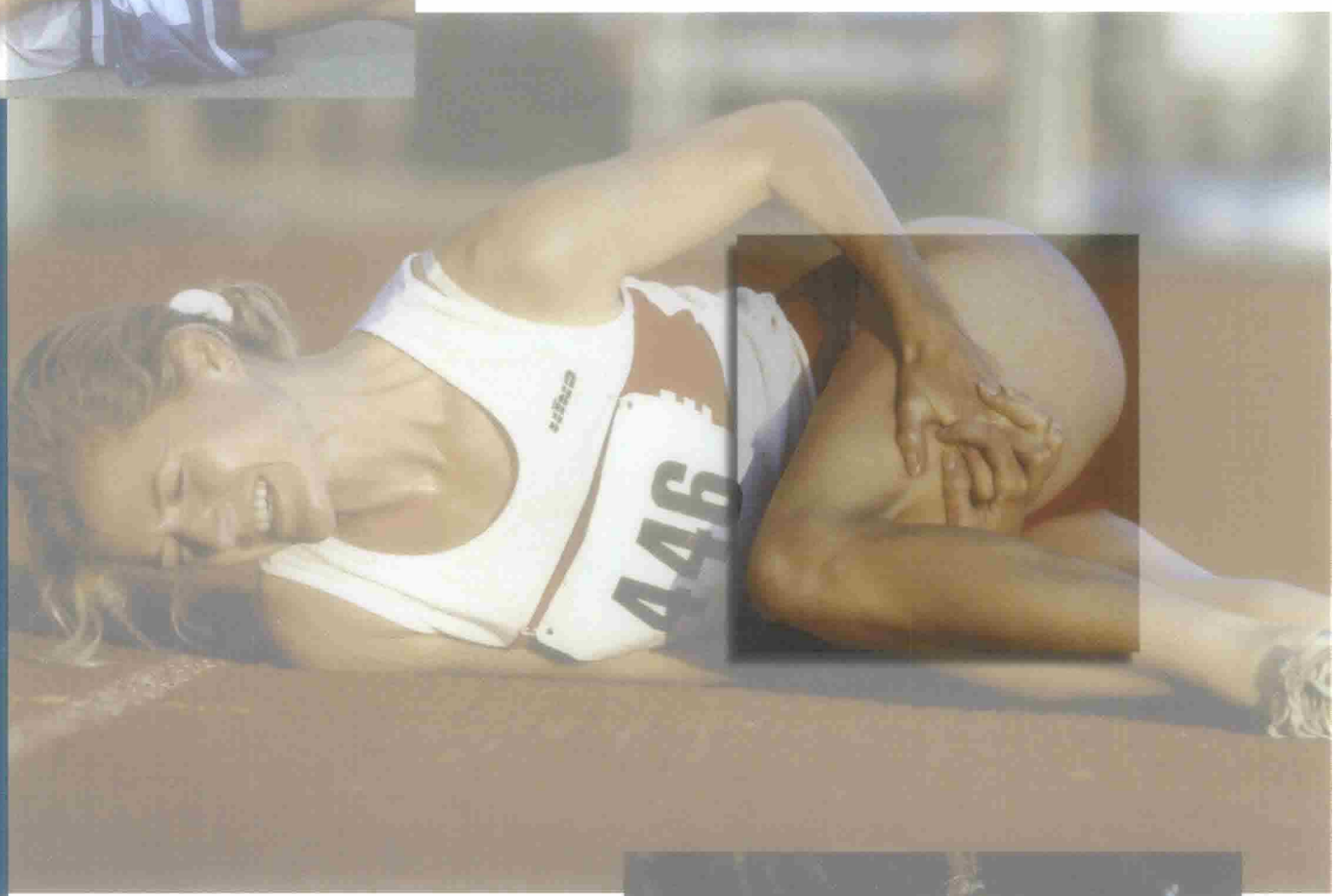
Acetaminophen is the most common cause of intentional and accidental poisoning in the United States today. The American Association of Poison Control Centers reported that there were more than 68,000 potential toxic exposures involving acetaminophen alone in 1994, and another 34,000 incidents involved acetaminophen in combination with other medications. Acetaminophen led the list of overdosing incidents with analgesics, ahead of ibuprofen and aspirin products. Of the acetaminophen-only poisonings, more than one fourth were intentional (suicide, abuse, and misuse), and more than half of acetaminophen-related deaths were suicides. Attempted suicide through acetaminophen overdosing is particularly common among adolescents.

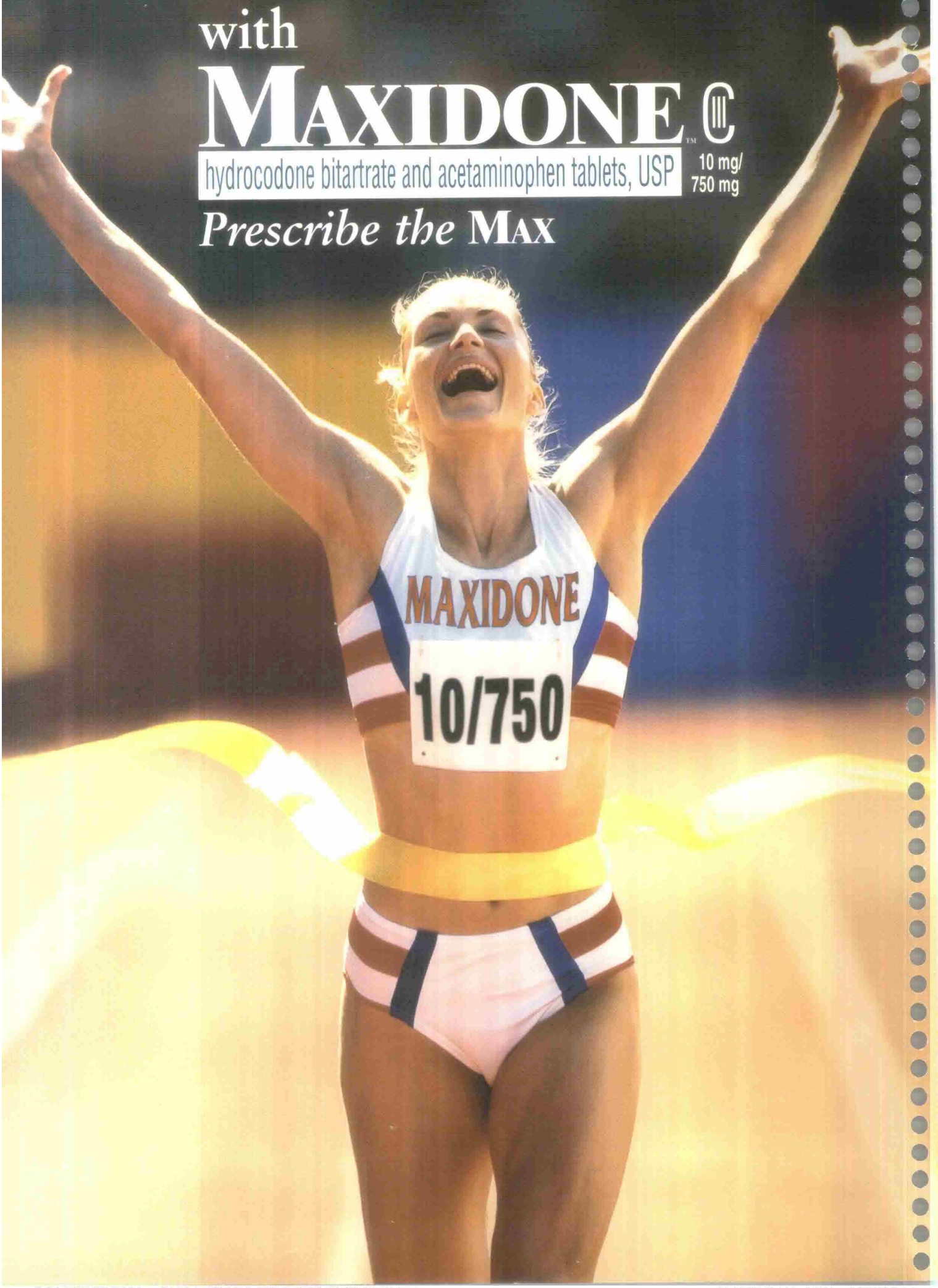
Most acetaminophen overdoses occur in children <6 years old—apparently when parents confuse the adult and pediatric preparations—and about 15% of cases occur in adults 19 years or older. Interestingly, toxicity occurs six times more frequently in adults with plasma levels of acetaminophen equal to those in children, presumably due to a faster turnover of glutathione in children.

The recommended adult dosage of acetaminophen is up to 1 g every 4 hours and no more than 4 g per day. This is equivalent to 325 to 650 mg (1 to 2 regular-strength tablets) 3 or 4 times a day; 500 to 1000 mg (1 to 2 extra-strength tablets) 3 or 4 times a day; or 650 to 1300 mg (1 to 2 extended-relief caplets) every 8 hours. The extended-relief caplets (650 mg) increase the potential for misuse, particularly among the elderly, because they closely resemble the extra-strength tablets (500 mg). Furthermore, appropriate treatment inadvertently may not be administered to patients who present less than 8 hours after ingestion. Due to the prolonged absorption of the extended-relief formulation, a toxic amount of acetaminophen may remain in the gastrointestinal tract and allow for an underestimation of acetaminophen levels needed to assess possible risk of hepatotoxicity.

In moderate to moderately severe pain

Pain has met its match...




with
MAXIDONE
hydrocodone bitartrate and acetaminophen tablets, USP
10 mg/
750 mg
Prescribe the MAX
MAXIDONE
10/750

The most potent hydrocodone/ acetaminophen combination available*

10 mg dose of hydrocodone is the highest available in a single tablet[1]

- The starting dose of hydrocodone in patients weighing >110 lbs in accordance with AHCPR guidelines†[2]
- Full agonist opioid
- Per tablet, contains 33% more hydrocodone than Vicodin ES®

750 mg dose of acetaminophen raises level of analgesia

- Enhances pain relief without reaching the maximum effective single dose for acetaminophen[3,4]
- Within the recommended 4-gram daily limit for acetaminophen use when prescribed at a maximum of 5 tablets daily[5]

Conveniently prescribed by telephone

- Schedule III designation allows call-in prescriptions and refills in most states, with no need for triplicate prescription blanks

Competitively priced to other brands in its class‡

Safety Information

The most frequently reported adverse effects include lightheadedness, dizziness, sedation, nausea, and vomiting. Hydrocodone may impair mental and/or physical abilities required for driving a car or operating machinery. Use with caution in elderly or debilitated patients.

*The highest strength combination of hydrocodone/acetaminophen available[1]

†In patients without renal or hepatic insufficiency, or other conditions affecting drug metabolism and kinetics

‡10 mg hydrocodone/acetaminophen combination products

Please see full prescribing information, which will be provided.

The most potent hydrocodone/acetaminophen combination available*

- ✳ The highest dose of hydrocodone and acetaminophen available in a single tablet[1]
- ✳ Enhances pain relief without reaching the maximum effective single dose for acetaminophen[3,4]
- ✳ Telephone prescribing convenience
- ✳ Competitively priced to other brands in its class†

Safety Information

The most frequently reported adverse effects include lightheadedness, dizziness, sedation, nausea, and vomiting. Hydrocodone may impair mental and/or physical abilities required for driving a car or operating machinery. Use with caution in elderly or debilitated patients.

MAXIDONE™ C III

hydrocodone bitartrate and acetaminophen tablets, USP 10 mg/750 mg

Prescribe the **MAX**

Not to be left behind. Property of Watson Pharma, Inc.
Full prescribing information will be provided.

*The highest strength combination of hydrocodone/acetaminophen available[1]
†10 mg hydrocodone/acetaminophen combination products

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1. *Physicians' Desk Reference®*. 54th ed. Montvale, NJ: Medical Economics Co. 2000. **2.** Acute Pain Management Guideline Panel. *Clinical Practice Guideline for Acute Pain Management: Operative or Medical Procedures and Trauma*. Rockville, MD: Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, Public Health Service; 1992. AHCPR publication 92-0032. **3.** Cooper SA, Precheur H, Rosenheck A, Ladov M, Engel J. Evaluation of oxycodone and acetaminophen in treatment of postoperative dental pain. *Oral Surg Oral Med Oral Pathol*. 1980;50(6):496–501. **4.** Skoglund LA, Skjelbred P, Fyllingen G. Analgesic efficacy of acetaminophen 1000 mg, acetaminophen 2000 mg, and the combination of acetaminophen 1000 mg and codeine phosphate 60 mg versus placebo in acute postoperative pain. *Pharmacotherapy*. 1991;11:364–369. **5.** United States Pharmacopeial Convention. *Drug Information for the Health Care Professional*. Vol. 1. Englewood, CO: Micromedex; 2000.

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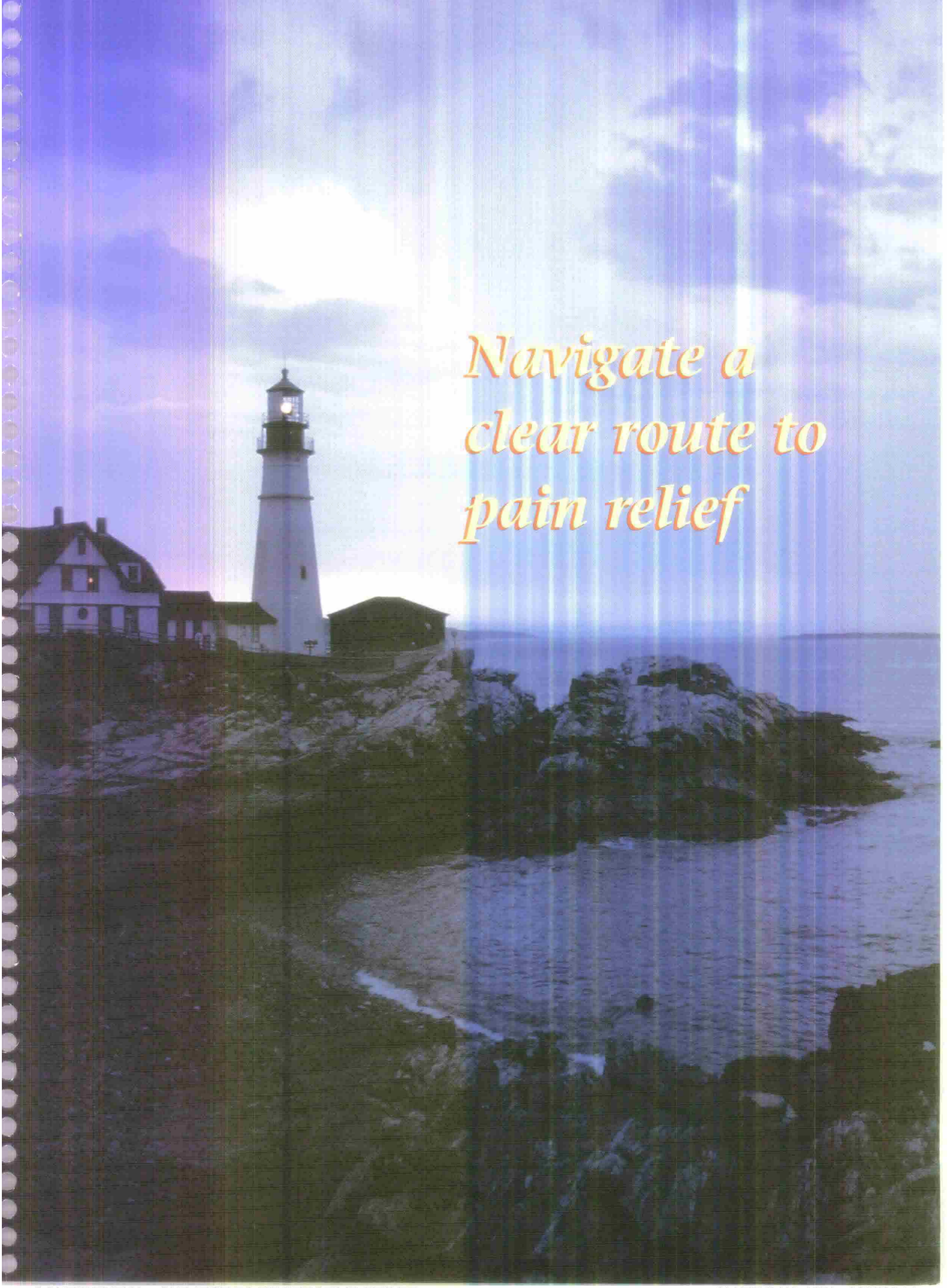
A Subsidiary of Watson Laboratories, Inc.

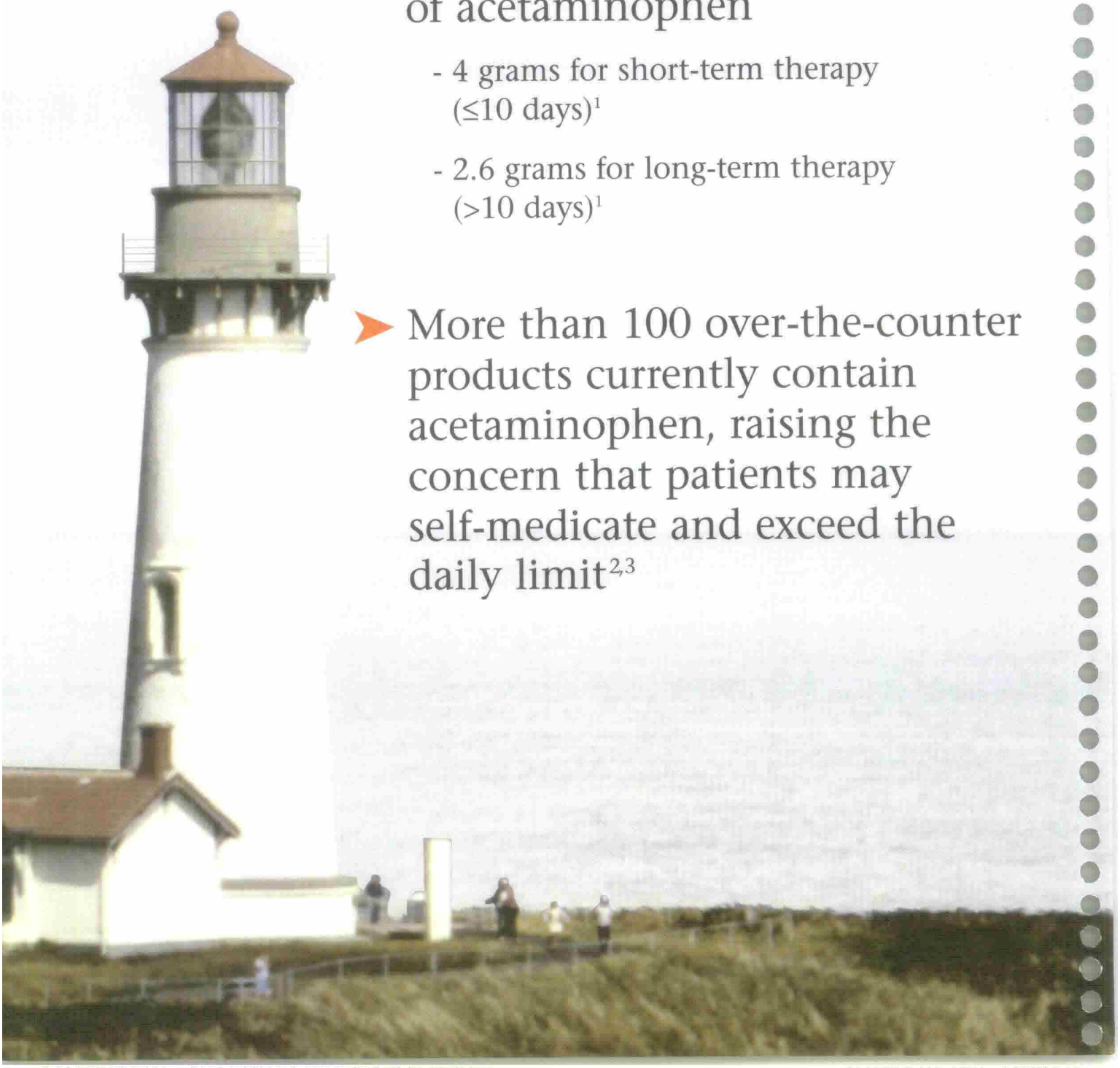
April 2001 01378


Navigate a
clear route to
pain relief

A low dose of acetaminophen

Acetaminophen—a closer look

- Recommended daily limit of acetaminophen
  - 4 grams for short-term therapy (≤10 days)[1]
  - 2.6 grams for long-term therapy (>10 days)[1]
- More than 100 over-the-counter products currently contain acetaminophen, raising the concern that patients may self-medicate and exceed the daily limit[2,3]

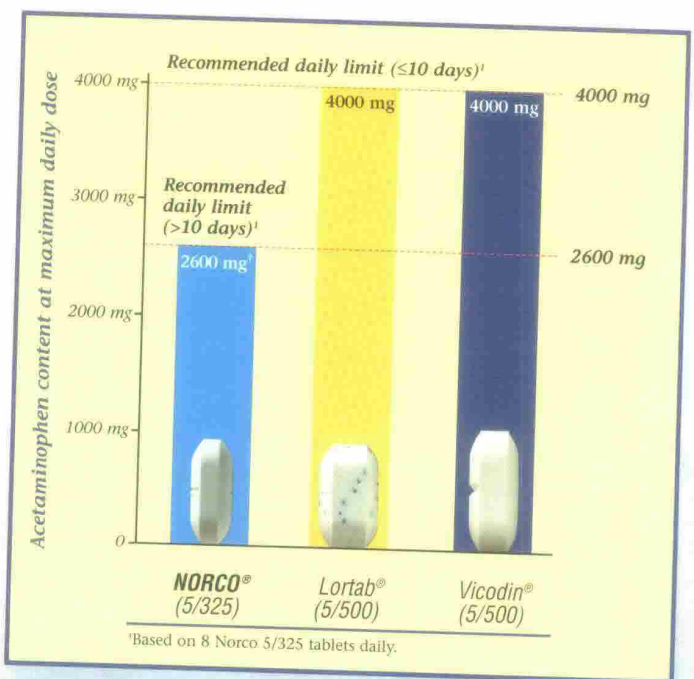


- Lower doses recommended in
  - Alcoholic patients[4,5]
  - Patients taking anticoagulant drugs[6]
  - Anorexic or fasting patients[4]
  - Patients with hepatic or renal disease[1]
- Chronic use of high doses associated with hepatotoxicity and end-stage renal disease[7,8]
- Over 64,000 incidents of accidental acetaminophen poisoning were reported in 1998[9]

NORCO® 5/325 ℞

5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

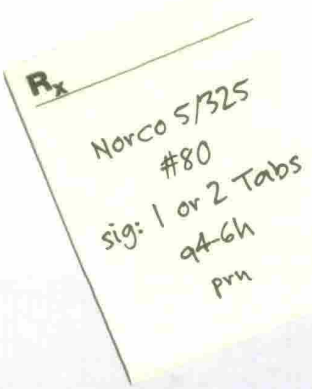
- Lowest level of acetaminophen*
  - May reduce concerns that patients will exceed the recommended 4 g daily limit (short-term therapy ≤10 days)[1] if taken with OTC products that contain acetaminophen
  - An appropriate level of acetaminophen for chronic pain (>10 days)[1]



Lortab® is a registered trademark of UCB Pharma, Inc.
Vicodin® is a registered trademark of Knoll Pharmaceutical Co.

- Demonstrated pain relief
  - Contains the #1 prescribed strength of hydrocodone[10]
- Smallest tablet size in its class*

- Telephone prescribing convenience
  - Schedule III designation allows call-in prescriptions and refills in most states, with no need for triplicate prescription blanks
- Competitively priced to other brands in its class*



NORCO® 5/325®

5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

*of all branded 5 mg hydrocodone/acetaminophen combination products

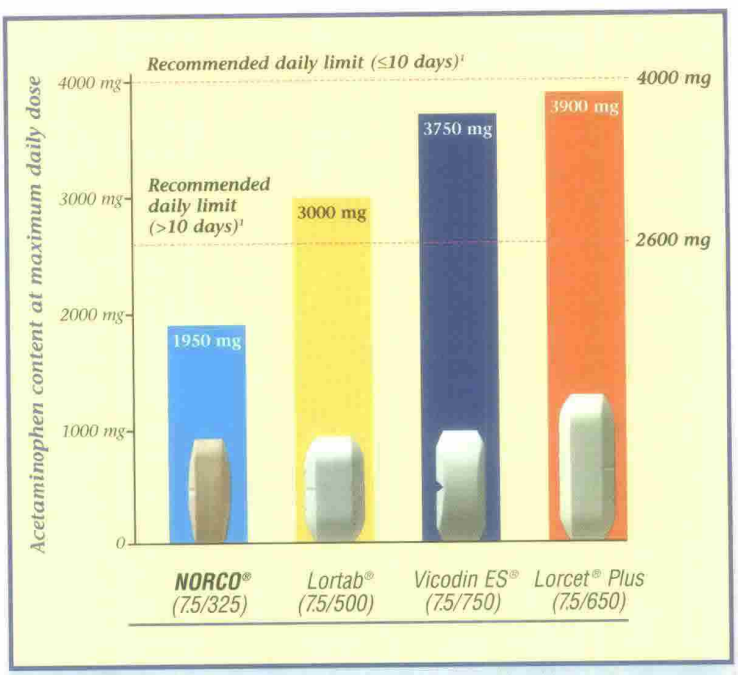
Safety Information

The most frequently reported adverse effects include lightheadedness, dizziness, sedation, nausea, and vomiting. Hydrocodone may impair mental and/or physical abilities required for driving a car or operating machinery.

NORCO® 7.5/325

7.5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

- Lowest level of acetaminophen*
  - May reduce concerns that patients will exceed the recommended 4 g daily limit (short-term therapy ≤10 days)[1] if taken with OTC products that contain acetaminophen
  - An appropriate level of acetaminophen for chronic pain (>10 days)[1]



Lorcet® Plus is a registered trademark of Forest Pharmaceuticals, Inc.
Lortab® is a registered trademark of UCB Pharma, Inc.
Vicodin ES® is a registered trademark of Knoll Pharmaceutical Co.

Demonstrated pain relief

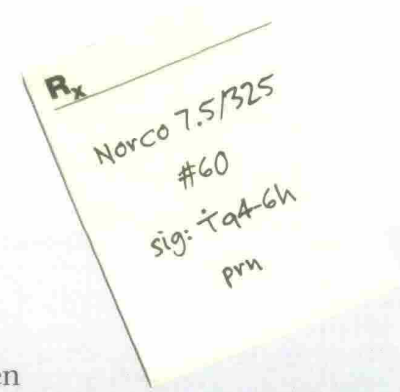
- At maximum daily dose, provides 20% more hydrocodone than Vicodin ES® on a daily basis

Smallest tablet size in its class*

Telephone prescribing convenience

- Schedule III designation allows call-in prescriptions and refills in most states, with no need for triplicate prescription blanks

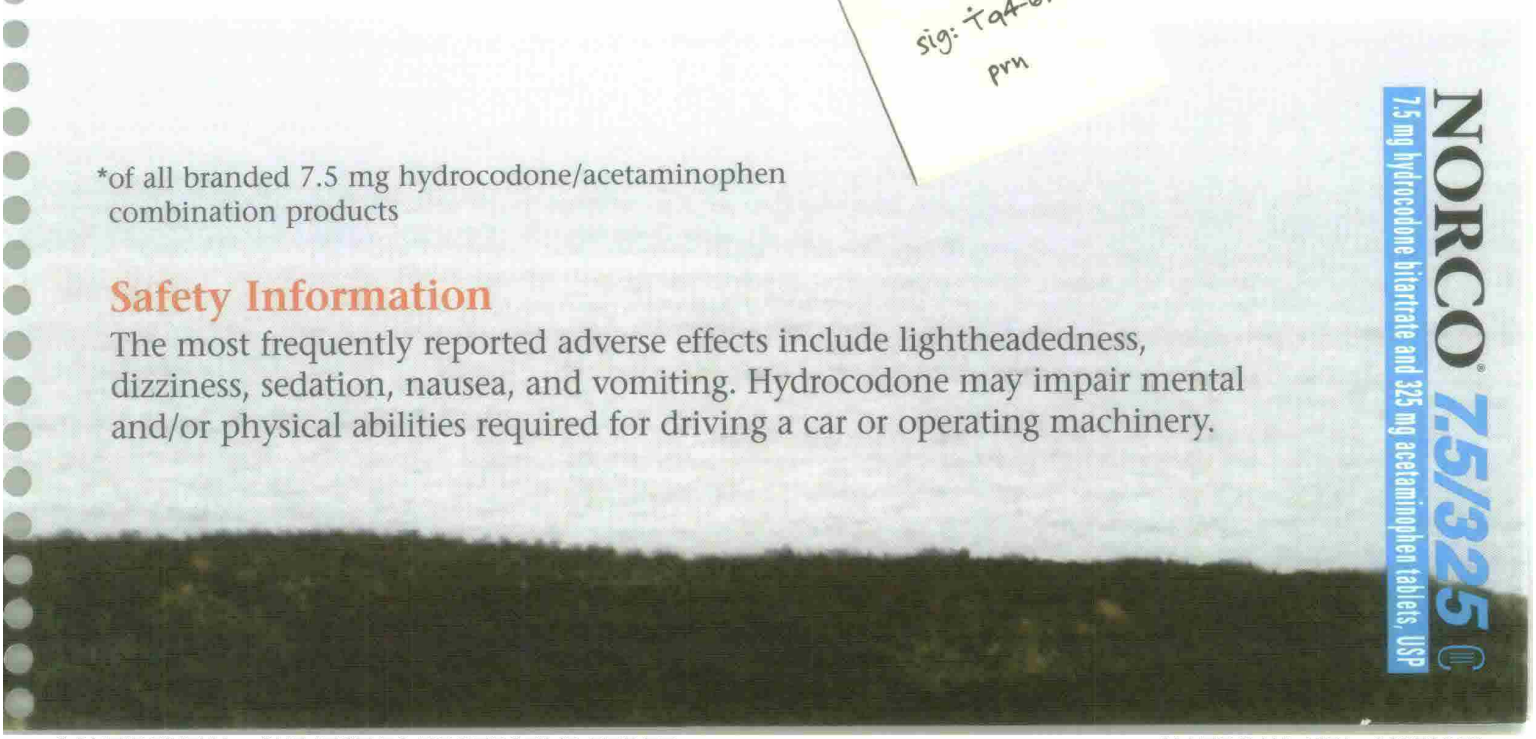
Competitively priced to other brands in its class*



*of all branded 7.5 mg hydrocodone/acetaminophen combination products

Safety Information

The most frequently reported adverse effects include lightheadedness, dizziness, sedation, nausea, and vomiting. Hydrocodone may impair mental and/or physical abilities required for driving a car or operating machinery.



NORCO® 5/325 C

5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

NORCO® 7.5/325 C

7.5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

- Lowest level of acetaminophen*
- Demonstrated pain relief
- Smallest tablet size in its class*
- Telephone prescribing convenience
- Competitively priced to other brands in its class*

Safety Information

The most frequently reported adverse effects include lightheadedness, dizziness, sedation, nausea, and vomiting. Hydrocodone may impair mental and/or physical abilities required for driving a car or operating machinery.

References

1. USP DI, 2000. *Drug Information for the Health Care Professional*. Englewood, CO: Micromedex, Inc; 2000. **2.** *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements™*. 21st ed. Montvale, NJ: Medical Economics Co. 2000. **3.** *2000 Drug Topics®. Red Book®*. Montvale, NJ: Medical Economics Co. 2000. **4.** Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA*. 1994;272(23):1845–1850. **5.** Zimmerman HJ, Maddrey WC. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: analysis of instances of therapeutic misadventure. *Hepatology*. 1995;22(3):767–773. **6.** Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA*. 1998;279:657–662. **7.** Tolman KG. Hepatotoxicity of non-narcotic analgesics. *Am J Med*. 1998;105(1B):13S–19S. **8.** Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1994;331:1675–1679. **9.** Litovitz TL, Klein-Schwartz W, Caravati EM, et al. 1998 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. 1999;435–487. **10.** *Source Prescription Audit*. Scott-Levin. Newtown, PA. September 2000.

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Not to be left behind.

Full prescribing information will be provided.

*of all branded 5 mg or 7.5 mg hydrocodone/acetaminophen combination products, respectively

WATSON Pharma, Inc.
A Subsidiary of Watson Laboratories, Inc.

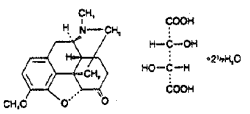
NORCO® 5/325®

5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

Rx only

DESCRIPTION

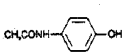
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration. **WARNING: May be habit forming** (see PRECAUTIONS, Information for Patients, and DRUG ABUSE AND DEPENDENCE). Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$

MW = 494.50

Acetaminophen, 4'-hydroxy-acetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$

MW = 151.17

Each Norco® 5/325 tablet contains: Hydrocodone Bitartrate ...5 mg
Acetaminophen .....325 mg

In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid and sugar spheres which are composed of starch derived from corn, sucrose, and FD&C Yellow #6.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy-metabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Norco® 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg /325 mg) are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, Norco® 5/325 tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Norco® 5/325 tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly. Alcohol and other CNS depressants may produce an additive CNS depression, when taken with the combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

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

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Norco® 5/325 tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

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

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Norco® 5/325 tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of Norco® 5/325 tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of Norco® 5/325 tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Norco® 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg /325 mg) are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, Norco® 5/325 tablets should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Norco® 5/325 tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

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

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain.

HOW SUPPLIED

Norco® 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) contain hydrocodone bitartrate 5 mg and acetaminophen 325 mg. They are supplied as white with orange specks, capsule-shaped, bisected tablets, debossed Watson on one side and 913 on the other side, in containers of 100 tablets, NDC 52544-913-01, in containers of 500 tablets, NDC 52544-913-05.

Storage: Store at controlled room temperature, 15°C to 30°C (59°F to 86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

A Schedule CIII Narcotic.

℞ only

Manufactured for
WATSON PHARMA, INC.
A subsidiary of
Watson Laboratories, Inc.
Corona, CA 92880
Manufactured by
Mikart, Inc.
Atlanta, GA 30318

Rev. 11/00 Code 0667C00

NORCO® 7.5/325 ©

7.5 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

NORCO® 10/325 ©

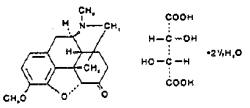
10 mg hydrocodone bitartrate and 325 mg acetaminophen tablets, USP

Rx only

DESCRIPTION

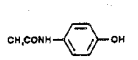
NORCO® (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$ M. W. = 494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ M. W. = 151.17

NORCO®, for oral administration is available in the following strengths:

	Hydrocodone Bitartrate	Acetaminophen
NORCO® 7.5/325	7.5 mg	325 mg
NORCO® 10/325	10 mg	325 mg

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, pregelatinized starch, povidone, and stearic acid; the 7.5 mg/325 mg tablets include FD&C Yellow #6 Aluminum Lake, the 10 mg/325 mg tablets include D&C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-ketoreduction to the corresponding 6-α- and 6-β-hydroxymetabolites. See **OVERDOSAGE** for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

NORCO® is indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

NORCO® should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, NORCO® should be used with caution in elderly or debilitated patients and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when NORCO® is used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

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

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

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

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: Teratogenic Effects: *Pregnancy Category C*: There are no adequate and well-controlled studies in pregnant women. NORCO® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of NORCO® may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on the brain stem respiratory centers (see **OVERDOSAGE**).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis. Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: NORCO® is classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when NORCO® is used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

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

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 6 tablets.

HOW SUPPLIED

NORCO® 7.5/325 is available as capsule-shaped, light orange tablets bisected on one side and debossed with "NORCO 729" on the other side. Each tablet contains 7.5 mg hydrocodone bitartrate and 325 mg acetaminophen. They are supplied as follows:

Bottles of 30	NDC 52544-729-30
Bottles of 100	NDC 52544-729-01
Bottles of 500	NDC 52544-729-05

NORCO® 10/325 is available as capsule-shaped, yellow tablets bisected on one side and debossed with "NORCO 539" on the other side. Each tablet contains 10 mg hydrocodone bitartrate and 325 mg acetaminophen. They are supplied as follows:

Bottles of 100	NDC 52544-539-01
Bottles of 500	NDC 52544-539-05

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

Watson Pharma, Inc.
a subsidiary of
Watson Laboratories, Inc., Corona CA 92880
Revised: May 2000 13897

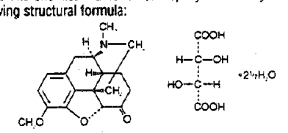
MAXIDONE™ C III

hydrocodone bitartrate and acetaminophen tablets, USP 10 mg/750 mg

DESCRIPTION

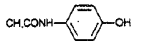
Maxidone™ (Hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2^1/_2H_2O$ MW=494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW=151.17

Each Maxidone™ tablet contains:

Hydrocodone Bitartrate	10 mg
Acetaminophen	750 mg

In addition, each tablet contains the following inactive ingredients: anhydrous lactose, croscarmellose sodium, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid, and D&C Yellow #10 Aluminum Lake.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See **OVERDOSAGE** for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See **OVERDOSAGE** for toxicity information.

INDICATIONS AND USAGE

Maxidone™ Tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

Maxidone™ Tablets should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, Maxidone™ Tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Maxidone™ Tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Maxidone™ Tablets, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

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

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

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

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Maxidone™ Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of Maxidone™ Tablets to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Maxidone™ Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of Maxidone™ Tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see **OVERDOSAGE**).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the **OVERDOSAGE** section.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Maxidone™ Tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, Maxidone™ Tablets should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when Maxidone™ Tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms

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

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dose should not exceed 5 tablets.

HOW SUPPLIED

Maxidone™ is supplied as a yellow, capsule-shaped tablet containing 10 mg hydrocodone bitartrate and 750 mg acetaminophen, bisected on one side and debossed with "Maxidone 634" on the other side.

Bottles of 100	NDC 52544-634-01
Bottles of 500	NDC 52544-634-05

Store at controlled room temperature, 15°C to 30°C (59°F to 86°F).
Dispense in a tight, light-resistant container with a child-resistant closure.

Rx only

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