Approved: March 5, 1997

MINUTES OF THE HOUSE COMMITTEE ON HEALTH AND HUMAN SERVICES.

The meeting was called to order by Chairperson Carlos Mayans, at 1:30 p.m. on February 17, 1997 in Room 423-S-of the State Capitol.

All members were present except: Representative Clark Shultz.

Committee staff present: Emalene Correll, Legislative Research Department
Norman Furse, Revisor of Statutes
Lois Hedrick, Committee Secretary

Conferees appearing before the committee:
Larry Froelich, Executive Secretary, Board of Pharmacy
Bob Williams, Executive Director, Kansas Pharmacists Association
Carol Macdonald, Administrative Secretary, Kansas Dental Board
Karen Braman, Social and Rehabilitation Services, Kansas City
Brad Smoot, Legislative Counsel for Johnson and Johnson
Dr. Tom Gibson, Ortho-McNeil Pharmaceutical
Steven Montgomery, Attorney, Representing Carter-Wallace, Inc.
Harold Riehm, Executive Director, Kansas Association of Osteopathic Medicine
Edward Letourneau, M.D., Rheumatologist, Cotton-O'Neil Clinic, Topeka
Meg Henson, Director of Government Affairs, Kansas Medical Society
Lawrence Buening, Jr., Executive Director, Kansas Board of Healing Arts

Others attending: See Guest List (Exhibit 1).

Chairperson Mayans opened the hearing on **HB 2225 - C-IV controlled substances.**

Bob Williams, of the Kansas Pharmacists Association, testified in support of HB 2225 by explaining that it would reclassify carisoprodol (SOMA), butorphanol (STADOL), and tramadol (ULTRAM) from non-controlled status to Schedule IV controlled drug status. He described the various listings of controlled drugs and the resultant administrative requirements (see testimony, Exhibit 2).

Larry Froelich, on behalf of the Board of Pharmacy, explained the reasoning for requesting that the three drugs be changed to a Schedule IV controlled substance classification and the required amendments to the law if the changes are to be enacted. (See testimony, Exhibit 3.) Mr. Froelich stated rescheduling these three drugs will not adversely affect the health of Kansans. He also explained that Johnson & Johnson is trying patient education to alleviate some of the Pharmacy Board's concerns and stated they had presented their plan to the board in September 1996, but the plan did not sway the Board's decision to request rescheduling.

Carol Macdonald, Kansas Dental Board, presented the Board's support of **HB 2225**, giving an example of abuse of butorphanol by one of their licensees,who actually volunteered the situation to the Board (see Exhibit 4).

Chairperson Mayans asked for questions of the conferees. Representative Hutchins asked if Kansas was the only state wanting to reschedule TRAMADOL. Mr. Williams answered that Arizona, Arkansas, Michigan, Missouri, Ohio, Oregon, Tennessee and Washington have them scheduled in Class IV. He stated that drug companies now include a warning that the drug may be abused; and that it was his belief the drug should be scheduled at level IV. Representative Geringer questioned why the relatively small incidence of possible abuse of TRAMADOL in the SRS research would cause the recommendation to reschedule, and had any contact been made with physicians or pharmacists to gain support of the changes. Mr. Froelich stated that the drug companies' inserts in the packages advising of the potential for abuse, strengthened by the SRS study, warrant the changes. He gave the example that Kansas was one of the first states to regulate steroids, and that was done even before the federal government did as well.

The Chairperson inquired about the areas of abuse of ULTRAM -- are they metropolitan or rural. Mr. Williams explained that currently they are "pocket" areas mainly in Sedgwick and Montgomery counties.

Karen Braman, with SRS, described the study recently conducted that indicated an increasing and inappropriate prescription of TRAMADOL to Medicaid recipients. In response to a question about abuse, Ms. Braman said SRS does not cut off assistance, but believes there should be guidelines to avoid abuse.

Meg Henson, Kansas Medical Society, questioned the reclassification of the drugs listed in **HB 2225**.

Brad Smoot, Legislative Counsel for Johnson & Johnson, presented testimony opposing the inclusion of tramadol (ULTRAM) in HB 2225 as it is their belief it is neither warranted or beneficial to patients and physicians. (See testimony, Exhibit 5).

Dr. Tom Gibson, of Ortho-McNeil Pharmaceutical, Raritan, N.J., presented testimony describing their product (tramadol) its history, use and established surveillance program to identify cases of abuse and their intervention to reduce abuse. Dr. Gibson expressed belief that the drug should not be on the schedule of controlled substances (see Exhibit 6).

Steven Montgomery, an attorney representing Carter-Wallace, Inc., presented testimony opposing the inclusion of carisoprodol (SOMA). He described the product's history, the requirements of the Kansas law to determine if a drug should be scheduled, and the potential of adversely affecting patients if it is scheduled (see Exhibit 7).

Harold Riehm, Kansas Association of Osteopathic Medicine, expressed the association's concerns with rescheduling the drugs (1) because of insufficient evidence of actual or potential abuse, (2) the elimination of sampling practices; and (3) lack of other evidence to support their inclusion (see Exhibit 8).

Edward Letourneau, M.D., Rheumotologist, Cotton-O-Neil Clinic, Topeka, expressed objections that he and his associate (J. Douglas Gardner, M.D.) have to the inclusion of ULTRAM and described the experience they have had with the drug (see Exhibit 9).

Chairperson Mayans then noted that Eric Voth, M.D., Internal Medicine and Addiction Medicine, Topeka, has submitted written testimony opposing the rescheduling of ULTRAM (see Exhibit 10).

There being no others present to testify on **HB 2225**, the hearing was closed.

The Chairperson then opened the hearing on **HB 2288 - treatment of obesity with controlled substances**.

Meg Henson, Kansas Medical Society, testified that the bill (which has been introduced at the request of the Society) will give the Board of Healing Arts the flexibility to regulate weight loss drugs, such as Redux. The Society believes that regulation of these drugs is necessary (see Exhibit 11).

Lawrence Buening, Jr., Kansas Board of Healing Arts, testified in support of **SB 2288** (see Exhibit 12).

There were no others present to testify on **HB 2288**, so the hearing was closed.

Chairperson Mayans called for action on **HB 2288**. On motion of Representative Morrison, seconded by Representative Gilmore, the committee passed **HB 2288** favorably, and that it be placed on the consent calendar. The motion was approved unanimously.

The meeting was adjourned at 3:00 p.m.

The next meeting is scheduled for February 18, 1997.

HOUSE COMMITTEE ON HEALTH AND HUMAN SERVICES COMMITTEE GUEST LIST
FEBRUARY 17, 1997

NAME	REPRESENTING
LARRY FROELICH	Board of Pharmacy
Bob Williams	KS Pharmacist Assoc.
Karen Braman	SRS
Dennis Mayans	—
Rolando Mayans	—
Harold Riehm	KAOM
Thomas P. Gibson	Ortho-Mc Neil
Brad Smoot	J & J
K.S. Reagan	Carter-Wallace
Steve Montgomery	Carter-Wallace
Carol Macdonald	Ks Dental Board
Amy Campbell	R. Rice Law Office
Susan Baker	
Myple Myers	Johnson + Johnson
Brian Smith	Johnson + Johnson
Edward Letourneau	Cotton-Oswald Clinic
Darin M Conklin	KPha
Rick Guthrie	Health Midwest
Michelle Peterson	PhRMA

HOUSE HEALTH/HUMAN SERVICES
Attachment 1-1
2 - 17 - 97

HOUSE COMMITTEE ON HEALTH AND HUMAN SERVICES COMMITTEE GUEST LIST
FEBRUARY 17, 1997

NAME	REPRESENTING
Ron Legino	DUR Board
LARRY BUENING	BOARD OF HEALING ARTS
Tricia Culley	Board of Healing Arts
[illegible]	[illegible]
Mark Stafford	Bd of Healing Arts

THE KANSAS PHARMACISTS ASSOCIATION
1308 SW 10TH AVENUE
TOPEKA, KANSAS 66604-1299
PHONE (913) 232-0439
FAX (913) 232-3764

ROBERT R. (BOB) WILLIAMS, M.S., C.A.E.
EXECUTIVE DIRECTOR

TESTIMONY

House of Representatives
Committee on Health and Human Services
February 17, 1997
HB 2225

My name is Bob Williams. I am the Executive Director of the Kansas Pharmacists Association. Thank you for this opportunity to address the Committee regarding HB 2225.

The Kansas Pharmacists Association is in support of HB 2225. This bill would reclassify Carisoprodol (SOMA), Butorphanol (STADOL) and Tramadol (ULTRAM) from a non-controlled status to a Schedule IV controlled drugs. Drugs which require a prescription are referred to as legend drugs (as opposed to over the counter--OTC--drugs). Scheduled drugs are controlled substances. All scheduled drugs are legend drugs. However, not all legend drugs are controlled drugs. There are five levels of controlled drugs. Drugs are "scheduled" based on their addictive and abuse potential with Schedule V being least addictive and Schedule I drugs most addictive. There are various restrictions which apply to "scheduled" drugs which do not apply to nonscheduled drugs. The restriction which most affects those patients who are taking scheduled drugs is the number of refills they may obtain before contacting the prescribing health care provider. Schedule IV drugs may not be filled or refilled more than six months after the date written for or be refilled more than five times. At that point the prescribing health care provider needs to be contacted to determine if the prescription drug may be filled again. This can be done verbally by the prescribing health care provider to the pharmacist. There is no limit on the number of refills for nonscheduled drugs except for those imposed by the prescribing health care provider. In addition, the **pharmacist** must maintain detailed records of the number of scheduled drugs he stocks, dispenses, returns or destroys. These requirements do not apply to nonscheduled drugs. Thus, drugs are scheduled due to their addictive qualities and their potential for abuse. It is the State Board of Pharmacy's position that due to the addictive qualities and their potential for abuse, these drugs should be Schedule IV controlled substances.

I have attached to my testimony information regarding Carisoprodol, Butorphanol and Tramadol. This information is from the American Hospital Formulary Service, one of the many reference books used by health care providers in identifying the various drugs available on today's market. I have underlined sections on the attached which you may want to pay particular attention to.

Carisoprodol (SOMA): You will note that this drug is structurally and pharmacologically related to meprobamate which is a Schedule IV drug. Carisoprodol has sedative and skeletal muscle relaxant effects. Listed under the "Chronic Toxicity" section you will note that overdosage produces symptoms similar to those of morphine overdosage and may include stupor, coma, shock, respiratory depression and even death. There is also a notation regarding

-over-

psychological dependence as a result of prolonged administration and caution should be used in patients who have histories of drug abuse.

Butorphanol (STADOL): This drug is a synthetic partial opiate agonist analgesic and is structurally related to morphine (a Schedule II drug) but pharmacologically similar to pentazocine (a Schedule IV drug) and nalbuphine (a nonscheduled drug). It has analgesic and opiate antagonistic effects and on a weight basis, the analgesic activity is approximately 4-7 times that of IM morphine. Like opiate agonists, it produces respiratory depression. Incidences and type of adverse effects of this drug are similar to those of opiate analgesics which are generally scheduled drugs. This is a relatively new drug on the market so the experience rating is less than Carisoprodol. It should be noted that when this drug was first introduced, usage was so widespread, it cost the Kansas Medicaid program $26,000 for just one month's use of this drug forcing the Medicaid Drug Utilization and Review Board to recommend "lock in" for any Medicaid recipient who exceeded the recommended dosage.

Tramadol (ULTRAM): While this drug's abuse potential appears to be low, because of the drug's opiate agonist activity it can produce dependence. At high doses, tramadol can produce respiratory depression and caution should be used in patients at risk for respiratory depression. Because of the high utilization rate of this drug by Medicaid patients, the Drug Utilization and Review Board is currently tracking this drug. I have attached a copy of their preliminary findings and a copy of the *DUR Bulletin* which addresses the concerns of the DUR Board.

In conclusion I would like to say that no busy health care practitioner welcomes the additional "hassle" required in prescribing or dispensing scheduled drugs. However, we doubt that any health care provider would argue that the principal consideration for determining whether to schedule a drug is the health care provider's convenience. Rather, we submit that heath care providers would agree that the principal consideration is the health and welfare of the patients who use these drugs. In addition all of the above-mentioned drugs are pain medications and there is a growing concern in this country that pain is under treated. Scheduling a given drug does not impede or limit a health care provider from prescribing pain management medication in whatever dose or duration he or she deems appropriate. It does require the prescribing health care provider to evaluate the appropriateness of continuing the patient on a prescribed pain medication after a given period of time. In this day and age, health care practitioners are forced to accept high volume in exchange for reduced reimbursement. Such environments can lead to patients falling through the cracks. Scheduling drugs is an additional "heads up" to busy practitioners which has the potential to improve patient outcomes.

Thank you.

bar... by continuous intrathecal infusion into a lumbar intrathecal space via a... implantable controlled-infusion device (pump). The manufacturer's labeling should be consulted for specialized administration techniques.

Baclofen concentrate for injection for intrathecal administration *must* only be diluted with sterile, preservative-free 0.9% sodium chloride injection. In the preparation of test doses of the drug for the purposes of drug-response screening, either concentration of the baclofen injection *must* be diluted to a concentration of 50 µg/mL prior to injection into the subarachnoid space. In patients receiving concentrations of the drug other than the commercially available strengths (i.e., 0.5 or 2 mg/mL), the injection also *must* be diluted.

As with other parenteral drug products, baclofen injection should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit.

■ Dosage

Oral Dosage

Oral dosage of baclofen should be individualized according to the patient's requirements and response using the lowest dosage that produces optimum response without adverse effects. Initially, low oral dosages of the drug should be administered.

For the management of spasticity, the initial oral dosage of baclofen is 5 mg 3 times daily. Oral daily dosage may be increased by 15 mg at 3-day intervals, until optimum effect is achieved (usually at dosages of 40–80 mg daily). In patients with psychiatric or brain disorders and in geriatric patients, oral dosage should be increased more gradually. In some patients, a smoother antispastic effect is obtained by administering the oral daily dosage in 4 divided doses. Some clinicians suggest that daily oral dosages of up to 150 mg are well tolerated and provide additional therapeutic benefit in some patients; however, the manufacturers state that total dosage should not exceed 80 mg daily. Some patients require 1–2 months of treatment for full benefit; however, the length of baclofen trial should be determined by the clinical state of the patient. Whenever baclofen is discontinued, daily dosage should be reduced slowly; abrupt withdrawal of baclofen may precipitate hallucinations and/or seizures, and acute exacerbation of spasticity.

Intrathecal Dosage

Following establishment of responsiveness to intrathecal baclofen (see Uses: Spasticity) and implantation of a compatible pump (e.g., SynchroMed® infusion system), the initial intrathecal dose of baclofen is twice the test dose that produced a positive response with a duration not exceeding 12 hours; this dose is infused intrathecally over 24 hours. For patients in whom a positive response to the test dose persisted for longer than 12 hours, the initial intrathecal dose is the same as the test dose that produced a positive response; this dose also is infused intrathecally over 24 hours. Following the initial infusion dose, the daily dose can be increased slowly by 10–30% increments at 24-hour intervals until the desired clinical response is achieved. If no substantive increase in response is observed with upward titration of intrathecal baclofen dosage, the function of the pump and patency of the catheter should be checked.

Adjustment of maintenance dosage often is needed during the initial months of intrathecal baclofen therapy as the patient adjusts to changes in life-style secondary to relief of spasticity. During periodic refills of the pump, the 24-hour dose may be increased by up to 10–40% as necessary to maintain adequate control of symptoms. In patients who develop intolerable adverse effects, the 24-hour maintenance dose can be decreased by 10–20%. During chronic therapy, gradual increases in dosage will be required in most patients to maintain optimal response. A sudden increase in dosage requirement should suggest the possibility of pump and/or catheter malfunction. Maintenance dosage during chronic intrathecal therapy has ranged from 12–1500 µg daily, with most patients responding adequately to 300–800 µg daily. There is only limited experience with intrathecal baclofen dosages of 1000 µg or more daily. Determination of optimum therapy requires individual titration. The lowest possible effective dosage should be employed.

During prolonged intrathecal baclofen therapy for spasticity, approximately 10% of patients become refractory to increasing dosages of the drug. While experience currently is insufficient to make firm recommendations regarding amelioration of such tolerance, patients occasionally have been hospitalized and subjected to a "drug holiday" in which intrathecal dosage was decreased gradually over a 2-week period, during which baclofen therapy was alternated with other methods of spasticity management. After a few days, sensitivity to baclofen may return and continuous intrathecal baclofen therapy may be resumed at the previously effective initial dosage.

For patients achieving relatively satisfactory relief via continuous intrathecal infusion employing an implantable pump, further benefit may be possible with more complex dosing schedules. For example, patients who commonly experience an exacerbation of spasticity at night that disrupts sleep may require a 20% increase in the hourly infusion rate; such changes should be programmed to begin approximately 2 hours before the time of desired clinical benefit.

The manual provided by the manufacturer of the implantable infusion device (i.e., pump) must be consulted for additional information, including specific instructions and precautions for programming the pump and/or refilling the reservoir, and recommendations for drug delivery specifications.

■ Dosage in Renal Impairment

Because baclofen is excreted principally in urine as unchanged drug, it may be necessary to reduce either oral or intrathecal dosage in patients with impaired renal function.

Preparations

Baclofen

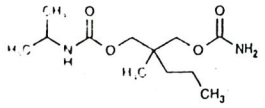
Oral		
Tablets	10 mg*	Lioresal® (with povidone; scored), Geigy
	20 mg*	Lioresal® (with povidone; scored), Geigy
Parenteral		
Concentrate for injection, for intrathecal administration via compatible infusion device or for intrathecal injection	0.5 mg/mL	Lioresal® Intrathecal (additive-free), Medtronic
	2 mg/mL	Lioresal® Intrathecal (additive-free), Medtronic

*available by nonproprietary name

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Carisoprodol

Carisoprodate
Isobamate
Isopropylmeprobamate



Chemistry and Stability

■ Chemistry

Carisoprodol, a centrally acting skeletal muscle relaxant, is structurally and pharmacologically related to meprobamate, mebutamate, and tybamate. Carisoprodol occurs as a white, crystalline powder with a bitter taste and a mild characteristic odor. The drug is very slightly soluble in water and freely soluble in alcohol. Carisoprodol has a pK_a of 4.2.

this is a C IV drug.

■ Stability

Carisoprodol tablets should be stored in well-closed containers at a temperature less than 40 C, preferably at 15–30°C.

Pharmacology

Carisoprodol is a CNS depressant which has sedative and skeletal muscle relaxant effects. The precise mechanism of action of the drug is not known. The skeletal muscle relaxant effects of orally administered carisoprodol are minimal and are probably related to its sedative effect. The drug does not directly relax skeletal muscle and, unlike neuromuscular blocking agents, does not depress neuronal conduction, neuromuscular transmission, or muscle excitability. In animals, carisoprodol appears to modify central perception of pain without abolishing peripheral pain reflexes and to have slight antipyretic activity, but these effects have not been demonstrated in clinical studies.

↳ American Hospital Formulary Service

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Pharmacokinetics

Absorption

Plasma concentrations of carisoprodol required for sedative, skeletal muscle relaxant, or toxic effects are not known. One manufacturer reports that plasma concentrations of 4–7 µg/mL were attained in 4 hours following oral administration of 350 mg of carisoprodol to healthy adults. Following usual therapeutic dosages, the onset of action is usually within 30 minutes and the duration of action is 4–6 hours.

Distribution

Carisoprodol crosses the placenta. The drug distributes into milk in concentrations 2–4 times higher than concurrent maternal plasma concentrations.

Elimination

The plasma half-life of carisoprodol is approximately 8 hours.

Carisoprodol is metabolized in the liver; animal studies indicate the drug may induce liver microsomal enzymes. Animal studies also indicate that the drug is excreted in urine, principally as hydroxycarisoprodol and hydroxymeprobamate, and to a lesser extent as meprobamate; trace amounts of carisoprodol are excreted unchanged in urine. The drug may be removed by hemodialysis or peritoneal dialysis.

Uses

Carisoprodol is used as an adjunct to rest, physical therapy, analgesics, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. Well-controlled clinical studies have not conclusively demonstrated whether relief of musculoskeletal pain by carisoprodol results from skeletal muscle relaxant effects, sedative effects, or a placebo effect of the drug. Most authorities attribute the beneficial effects of carisoprodol to its sedative properties. The drug is ineffective in the treatment of skeletal muscle hyperactivity secondary to chronic neurologic disorders, such as cerebral palsy, and other dyskinesias.

Cautions

Nervous System Effects

The most frequent adverse effects of carisoprodol are drowsiness and dizziness. Other adverse CNS effects include vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia.

Sensitivity Reactions

Occasionally, patients may have allergic or idiosyncratic reactions to carisoprodol. In patients who have not received carisoprodol previously, these reactions are usually evident by the time of the fourth dose of the drug. Idiosyncratic reactions may be characterized by extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. These symptoms usually subside within several hours; however, symptomatic and supportive therapy, including hospitalization, may be necessary in some patients. (See Cautions: Precautions and Contraindications.) Rash, erythema multiforme, pruritus, urticaria, eosinophilia, and fixed drug eruption have occurred in patients receiving carisoprodol who previously had similar reactions to meprobamate. Severe allergic reactions have been characterized by asthmatic episodes, fever, weakness, dizziness, angioedema, smarting eyes, hypotension, and anaphylactic shock.

Other Adverse Effects

Adverse GI effects of carisoprodol include nausea, vomiting, hiccups, increased bowel activity, and epigastric distress. Adverse cardiovascular effects include tachycardia, postural hypotension, and facial flushing. Although a causal relationship to carisoprodol has not been established, leukopenia and pancytopenia have occurred rarely in patients receiving carisoprodol along with other drugs.

Precautions and Contraindications

Because carisoprodol is metabolized by the liver and excreted by the kidneys, the drug should be used with caution in patients with impaired hepatic or renal function. Patients should be warned that carisoprodol may impair ability to perform hazardous activities requiring mental alertness or physical coordination such as operating machinery or driving a motor vehicle.

Commercially available formulations of carisoprodol (e.g., Soma® Compound with Codeine) may contain sodium metabisulfite, a sulfite that can cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown but probably low; such sensitivity appears to occur more frequently in asthmatic than in nonasthmatic individuals.

If allergic or idiosyncratic reactions occur during carisoprodol t[illegible] the drug should be discontinued and appropriate symptomatic therapy (such as epinephrine, antihistamines, and/or corticosteroids) given if needed.

Carisoprodol is contraindicated in patients with acute intermittent porphyria and in patients who have previously demonstrated allergic or idiosyncratic reactions to carisoprodol or related compounds such as meprobamate, mebutamate, or tybamate.

Pediatric Precautions

Safety and efficacy of carisoprodol in children younger than 12 years of age have not been established; therefore, the drug should not be administered to children in this age group.

Pregnancy and Lactation

Safe use of carisoprodol during pregnancy or lactation has not been established. The drug should not be used in women who are or may become pregnant or in nursing women unless the possible benefits outweigh the potential risks. If carisoprodol is used in nursing women, the fact that the drug may distribute into milk in a concentration 2–4 times that of maternal plasma concentrations should be kept in mind.

Chronic Toxicity

Daily ingestion of very large doses of carisoprodol (100 mg/kg for an unspecified number of days) has produced mild withdrawal symptoms such as abdominal cramps, insomnia, chilliness, headache, and nausea when the drug was abruptly discontinued. Psychological dependence has been reported rarely with prolonged administration of usual adult doses, and the drug should be used with caution in patients who have histories of drug abuse.

Acute Toxicity

Manifestations

Carisoprodol overdosage produces symptoms which are similar to those of meprobamate overdosage and may include stupor, coma, shock, respiratory depression, and, very rarely, death. One man who ingested 8.4 g of carisoprodol and another who ingested 9.45 g had maximum plasma concentrations of 37 and 38 µg/mL, respectively. In these patients, drowsiness, dizziness, headache, diplopia, and nystagmus on lateral gaze occurred. Treatment consisted of supportive therapy, gastric lavage, and emesis; recovery was uneventful.

Treatment

Although limited information is available on the treatment of carisoprodol intoxication, treatment of meprobamate intoxication consists of general supportive therapy including maintenance of adequate airway, assisted respiration, and cautious administration of pressor agents, such as metaraminol or norepinephrine, if necessary. If the patient is comatose, gastric lavage may be done if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. If the patient is fully conscious, emesis should be induced. Activated charcoal may be instilled after gastric lavage and/or emesis to adsorb any remaining drug, since relapse and death attributable to incomplete gastric emptying and delayed absorption may occur. Urinary output should be monitored and overhydration avoided. Forced diuresis with an osmotic diuretic such as mannitol and/or peritoneal dialysis or hemodialysis may be beneficial.

Drug Interactions

CNS Depressants

Additive CNS depression may occur when carisoprodol is administered concomitantly with other CNS depressants, including alcohol. If carisoprodol is used concomitantly with other depressant drugs, caution should be used to avoid overdosage.

Dosage and Administration

Administration

Carisoprodol is administered orally.

Dosage

The usual adult dosage of carisoprodol is 350 mg 3 times daily and at bedtime. If adverse CNS effects are severe, dosage should be reduced.

Although the manufacturers state that safety and efficacy of carisoprodol in children younger than 12 years of age have not been established, some clinicians have suggested a dosage of 25 mg/kg or 750 mg/m² daily in 4 divided doses for children 5 years of age or older.

phine therapy alone. In a group of patients who received a single, high dose of buprenorphine before undergoing cholecystectomy with balanced anesthesia and experienced pain in the immediate postoperative phase, addition of naloxone reportedly resulted in adequate analgesia, possibly by counteracting dominant antagonistic effects of buprenorphine.

Respiratory and cardiovascular collapse has occurred in several patients receiving usual doses of IV buprenorphine and oral diazepam concomitantly; the patients recovered following treatment that included assisted respiration and IV doxapram. Bradycardia, respiratory depression, and prolonged drowsiness occurred following IV administration of buprenorphine during surgery in a patient who had received oral lorazepam preoperatively. The patient recovered following treatment that included IV atropine and assisted respiration; however, drowsiness persisted for more than 12 hours, and lack of awareness and recall of the surgical procedure (amnesia) reportedly lasted for 48 hours.

■ Other Drugs

When buprenorphine is administered concomitantly with a drug(s) that may reduce hepatic blood flow (e.g., halothane) and thereby reduce hepatic elimination of the partial opiate agonist, the activity of buprenorphine may be increased and/or prolonged. If such concomitant therapy is administered, buprenorphine should be used with caution and dosage of at least one of the drugs should be reduced.

Because monoamine oxidase (MAO) inhibitors may be additive with or may potentiate the action of CNS depressants, buprenorphine and an MAO inhibitor should be administered concomitantly with caution. Buprenorphine may also potentiate the effects of local anesthetics (e.g., bupivacaine hydrochloride, mepivacaine hydrochloride), and concomitant administration of the drugs may result in a more rapid onset and prolonged duration of analgesia.

Concomitant administration of buprenorphine and a coumarin anticoagulant (phenprocoumon, no longer commercially available) reportedly has been associated with a purpuric response.

Dosage and Administration

■ Administration

Buprenorphine hydrochloride is administered by IM or slow (over a period of at least 2 minutes) IV injection. The drug has also been administered by continuous IV infusion†, by IM or IV injection using a patient-controlled infusion device†, and by epidural injection†. Buprenorphine hydrochloride has also been administered sublingually†, but a sublingual dosage form of the drug is currently not commercially available in the US.

For continuous IV infusion†, buprenorphine hydrochloride injection has been diluted to a concentration of 15 µg/mL in 0.9% sodium chloride and administered via a controlled-infusion device. For continuous IV infusion†, the drug should be administered only by qualified individuals familiar with the technique and patient management problems (i.e., respiratory depression) associated with buprenorphine administration. For epidural injection†, buprenorphine hydrochloride injection has been diluted to a concentration of 6–30 µg/mL in 0.9% sodium chloride.

Buprenorphine hydrochloride injection and diluted solutions of the drug should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ Dosage

Dosage of buprenorphine hydrochloride is expressed in terms of buprenorphine. Dosage of buprenorphine should be adjusted according to the severity of pain, physical status of the patient, and other drugs that the patient is receiving.

Pain

For the relief of moderate to severe pain, the usual IM or IV dosage of buprenorphine in patients 13 years of age and older is 0.3 mg given at intervals of up to every 6 hours as necessary. The initial dose (up to 0.3 mg) may be repeated once in 30–60 minutes, if needed. The manufacturer recommends that buprenorphine dosage be decreased by 50% in patients who are at increased risk of respiratory depression (see Cautions: Precautions and Contraindications). Particular caution is necessary if the drug is administered IV, especially with initial doses. In some patients, it may be necessary to increase the dose up to 0.6 mg and/or reduce the dosing interval (e.g., every 4 hours), but the manufacturer recommends that such relatively high doses *only* be administered IM and *only* to adults who are not at increased risk of respiratory depression. In some patients, a dosing interval greater than 6 hours may be adequate. For the management of postoperative pain, a recommended regimen is an initial dose of 0.3 mg IM, repeated once after 30–60 minutes and then every 4–6 hours as necessary. Alternatively, a regimen including an initial dose of 0.3 mg of buprenorphine followed by another 0.3-mg dose repeated in 3 hours has been shown to be as effective as a single 0.6-mg dose in relieving postoperative pain. There are insufficient clinical data to recommend single doses greater than 0.6 mg for long-term use.

Although children 2–12 years of age have received buprenorphine dosages of 2–6 µg/kg every 4–6 hours, longer dosing intervals (e.g., every 6–8 hours) may be sufficient for some children and a fixed around-the-clock dosing interval should not be used until an adequate dosing interval has been established by clinical observation of the patient. In addition, the manufacturer states that there are insufficient data in children 2–12 years of age to recommend buprenorphine doses exceeding 6 µg/kg or administration of a repeat dose within 30–60 minutes of the initial dose.

When buprenorphine was administered by continuous IV infusion† in the management of postoperative pain, dosages of 25–250 µg/hour have been used in adults.

Buprenorphine has been administered epidurally† in the management of postoperative pain in single doses of 60 µg, up to a mean total dose of 180 µg administered over a 48-hour period. Buprenorphine has also been administered epidurally† in a dose of 0.3 mg as a supplement to surgical anesthesia with a local anesthetic. In the management of severe, chronic pain (e.g., in terminally ill patients), buprenorphine doses of 0.15–0.3 mg have been administered epidurally as frequently as every 6 hours up to a mean total daily dose of 0.86 mg (range: 0.15–7.2 mg).

In children 9 months to 9 years of age† undergoing circumcision, some clinicians have used an initial IM buprenorphine dose of 3 µg/kg as an adjunct to surgical anesthesia followed by additional 3-µg/kg doses as necessary to provide analgesia postoperatively.

Other Uses

To reverse fentanyl-induced anesthesia† and provide subsequent analgesia in adults, IV or IM buprenorphine doses of 0.3–0.8 mg have been administered 1–4 hours following induction of anesthesia and about 30 minutes prior to the end of surgery.

Preparations

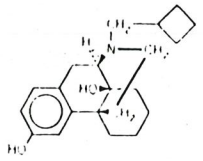
Buprenorphine hydrochloride is subject to control under the Federal Controlled Substances Act of 1970 as a schedule V (C-V) drug.

Buprenorphine Hydrochloride

Parenteral Injection	0.3 mg (of buprenorphine) per mL	Buprenex® (C-V), Reckitt & Colman

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Butorphanol Tartrate



butorphanol

Not a controlled drug

This is C II

This is C II

Chemistry and Stability

■ Chemistry

Butorphanol tartrate is a synthetic partial opiate agonist analgesic. The drug is structurally related to morphine but pharmacologically similar to pentazocine and nalbuphine. Butorphanol tartrate occurs as a white powder with a bitter taste and is sparingly soluble in water and insoluble in alcohol. The pK_a of the drug is 8.6.

Butorphanol tartrate is commercially available as an injection and as a solution for nasal inhalation. Butorphanol tartrate injection is a sterile solution of the drug in water; the injection contains sodium citrate and has a pH of 3–5.5. For intranasal use, butorphanol tartrate is available as a solution of the drug in purified water; sodium hydroxide and/or hydrochloric acid are added to adjust pH to 5. Butorphanol tartrate injection and nasal solution contain sodium chloride to adjust tonicity and citric acid; the multiple-dose vials of the injection and nasal solution also contain benzethonium chloride as a preservative. Butorphanol tartrate nasal solution is administered by a spray pump which, after initial priming, delivers metered sprays containing 1 mg of butorphanol tartrate per spray.

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Butorphanol tartrate injection should be protected from light and stored at temperatures below 30°C; freezing should be avoided. Butorphanol tartrate nasal solution should be stored at temperatures below 30°C.

Butorphanol tartrate is reportedly physically and chemically compatible for at least 24 hours with atropine sulfate, hydroxyzine hydrochloride, or promethazine hydrochloride. Specialized references should be consulted for specific compatibility information.

Pharmacology

Butorphanol tartrate has analgesic and opiate antagonistic effects. The exact mechanisms of actions of the drug are not known. However, the analgesic effect is believed to result from an interaction with an opiate receptor site in the CNS (probably in or associated with the limbic system); the opiate antagonistic effect may result from competitive inhibition at the opiate receptor, but other mechanisms probably also are involved. The drug exerts antagonistic or partially antagonistic effects at μ opiate receptor sites, while it is thought that butorphanol exerts its agonistic effects principally at the κ and σ opiate receptors. On a weight basis, the analgesic activity of IM butorphanol tartrate is approximately 4–7 times that of IM morphine, 15–30 times that of IM pentazocine, and 30–50 times that of IM meperidine. Studies in animals indicate that, on a weight basis, subcutaneous butorphanol has 30 times the opiate antagonist activity of subcutaneous pentazocine and 1/40 that of subcutaneous naloxone.

Like opiate agonists, butorphanol produces respiratory depression, sedation, miosis and, in animals, antitussive effects. In adults, a single 2-mg IV dose of butorphanol tartrate (about 0.03 mg/kg) decreases respiration to the same degree as 10 mg of morphine sulfate IV or 70 mg of meperidine hydrochloride IV. In contrast to morphine, respiratory depression in healthy adults plateaus with a 2-mg IV dose of butorphanol tartrate. However, the duration of respiratory depression produced by butorphanol is increased with increasing dosage (i.e., respiratory depression persists 1 hour after 2 mg IV and at least 90 minutes after 4 mg IV).

In one study, IV administration of butorphanol tartrate 0.025 mg/kg slightly increased pulmonary artery pressure, pulmonary wedge pressure, left ventricular end-diastolic pressure, systemic arterial pressure, pulmonary vascular resistance, and cardiac index.

In animals, butorphanol tartrate inhibits GI motility slightly, causes little increase in duodenal smooth muscle activity, and has little or no effect on bile duct flow. In dogs, butorphanol causes very little systemic histamine release as compared to equianalgesic doses of morphine. In contrast to morphine, butorphanol transiently increases urine output and decreases urine osmolality and sodium and potassium excretion in rats. These effects are caused by inhibition of release of vasopressin from the hypothalamus.

IV administration of 0.2–0.8 mg of naloxone hydrochloride reverses the respiratory depressant effects of 2–4 mg of IV butorphanol tartrate. Naloxone also reverses the analgesic, antitussive, and GI motility inhibiting effects of butorphanol; the diuretic response to butorphanol in animals is *not* reversed by naloxone.

Pharmacokinetics

Absorption

Butorphanol tartrate is completely absorbed from the GI tract in healthy, fasting individuals and from IM injection sites. However, orally administered butorphanol tartrate undergoes first-pass metabolism and only 17% of a dose reaches systemic circulation unchanged. The absolute bioavailability of butorphanol following nasal inhalation may vary with age and gender; the absolute bioavailability of the nasal solution is about 50, 70, and 75% in geriatric women, young individuals, and geriatric men, respectively. Absolute bioavailability of nasally inhaled butorphanol appears to be unchanged in patients with allergic rhinitis. However, in patients receiving a nasal vasoconstrictor (e.g., oxymetazoline), rate of absorption of intranasal butorphanol may be decreased while extent of absorption appears to be unchanged. When intranasal butorphanol was administered in patients receiving oxymetazoline, peak plasma concentrations of butorphanol were reduced by about 50%.

Following oral administration of a single 8-mg dose of butorphanol tartrate to healthy, fasting individuals, peak plasma butorphanol concentrations of 0.7 ng/mL are achieved within 1–1.5 hours. Peak plasma butorphanol concentrations of approximately 2.2 ng/mL occur 30–60 minutes after IM administration of a single 2-mg dose. Peak plasma concentrations of 1.5 ng/mL occur almost immediately after a single 1-mg IV dose. Following nasal inhalation of a single 1-mg dose of butorphanol tartrate solution, mean peak blood butorphanol concentrations of 0.9–1.04 ng/mL are achieved in about 30–60 minutes. Butorphanol tartrate appears to exhibit dose-proportional, linear pharmacokinetics following inhalation of 1–4 mg of nasal solution of the drug every 6 hours for 5 days; peak plasma concentrations and the area under the plasma concentration-time curve (AUC) increased in a dose-dependent fashion, while time to achieve peak plasma concentrations remained relatively constant. Steady-state plasma concentrations of nasally inhaled butorphanol were reached within 48 hours and were about 1.8 times those reported following administration of single doses of the nasal solution; therefore, modest accumulation of the drug appears to occur. After an initial absorption/distribution phase, single-dose pharmacokinetics of butorphanol are similar following IV, IM, or intranasal administration.

After IV administration of 1 or 2 mg of butorphanol tartrate in postoperative patients, the onset of analgesic activity occurs in 1 minute, peak analgesia occurs in 4–5 minutes, and the duration of action is 2–4 hours. Following IM administration of 1 or 2 mg of butorphanol tartrate in postoperative patients, analgesic activity occurs within 10–30 minutes, peak analgesia occurs within 30–60 minutes, and duration of analgesia is 3–4 hours; after 4 mg IM, analgesic effects usually persist at least 4 hours. After nasal inhalation of 1 or 2 mg of butorphanol tartrate solution in postoperative patients, onset of analgesia occurs within 15 minutes, peak analgesia occurs in about 1–2 hours, and duration of analgesia is approximately 2.5–5 hours. In one study, oral administration of 8 or 16 mg of butorphanol tartrate produced analgesic effects within 1–2 hours and analgesia persisted 5–6 hours.

Distribution

Animal studies indicate that highest concentrations of butorphanol and its metabolites are found in the liver, kidneys, and intestine; drug concentrations are higher in the lungs, spleen, heart, endocrine tissues, blood cells, and fat tissue than in plasma; brain concentrations are lower than plasma concentrations. In concentrations of 1–7 ng/mL, about 80% of butorphanol is bound to plasma proteins. Following IV administration, the mean volume of distribution of butorphanol is 487 (range: 305–901 L) and 552 L (range: 305–737 L) in young (20–40 years of age) and geriatric individuals (older than 65 years of age), respectively.

Butorphanol rapidly crosses the placenta, and neonatal serum concentrations are 0.4–1.4 times maternal concentrations. The drug is distributed into milk.

Elimination

Plasma elimination half-life of butorphanol is similar following intranasal and IV administration; the plasma elimination half-life of butorphanol is about 4.6 (range: 2–8.7 hours) and 4.7 hours (range: 2.9–8.8 hours) after IV and intranasal administration, respectively. Plasma elimination half-life of butorphanol may be increased in geriatric individuals following IV and intranasal administration; elimination half-life reportedly was about 5.6 (range 3.3–8.8 hours) and 6.6 hours (range: 3.8–9.2 hours) following IV and intranasal administration, respectively. Plasma elimination half-life also may be increased in patients with renal impairment (creatinine clearance less than 30 mL/minute); elimination half-life reportedly was 10.5 hours in such patients.

Butorphanol is extensively metabolized in the liver, principally by hydroxylation to form hydroxybutorphanol, the major metabolite; *N*-dealkylation and conjugation of butorphanol and its metabolites also occur. Metabolites of butorphanol have no analgesic activity. Butorphanol and its metabolites are excreted mainly by the kidneys as unconjugated hydroxybutorphanol (60–80% of a dose), and less than 5% of a dose is excreted unchanged in urine. In 72–96 hours, 62% of a 1-mg IV dose, 72% of a 2-mg IM dose, and 75% of an 8-mg oral dose can be recovered in the urine. Glucuronides of butorphanol and/or hydroxybutorphanol are excreted in bile and undergo enterohepatic recycling. About 11–14% of a parenteral dose is excreted in the feces. Following IV administration of butorphanol tartrate, mean total body clearance of butorphanol is 1650 (range: 1167–2567 mL/minute) and 1367 mL/minute (range: 867–2383 mL/minute) in young (20–40 years of age) and geriatric (older than 65 years of age) individuals, respectively. Body clearance of butorphanol also may be decreased in patients with renal impairment. Following administration of butorphanol tartrate nasal solution, total body clearance of butorphanol is about 4333 and 2500 mL/minute in healthy individuals and in patients with renal impairment (those with creatinine clearance less than 30 mL/minute), respectively.

Uses

Butorphanol tartrate injection is used as an analgesic in the treatment of moderate to severe pain such as that associated with acute and chronic medical disorders including cancer, neuropathic or spastic conditions, orthopedic problems, burns, renal colic, and surgery. Butorphanol tartrate injection also is used to provide preoperative sedation and analgesia and as a supplement to surgical anesthesia. However, butorphanol should be used with caution in patients undergoing surgery of the biliary tract. Butorphanol tartrate injection also is used for obstetric analgesia during labor.

In equianalgesic doses, parenteral butorphanol is as effective as morphine, meperidine, and pentazocine, but determination of the relative potential for abuse of butorphanol must await further studies and more extensive use of the drug.

Butorphanol tartrate nasal solution is used as an analgesic for the relief of moderate to severe postoperative (including that associated with orthopedic

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surgery), postpartum, and orthopedic (including musculoskeletal) pain. Butorphanol tartrate nasal solution also is used for the management of migraine headache. When used to relieve postoperative pain, single intranasal butorphanol tartrate doses of 1 or 2 mg have been as effective as IM meperidine hydrochloride doses of 37.5 or 75 mg, respectively. When used to relieve migraine headache, butorphanol tartrate nasal solution administered as two 1-mg doses (given 1 hour apart) was as effective as a single 10-mg dose of IM methadone hydrochloride.

Because it does not suppress the abstinence syndrome and may induce withdrawal in opiate-dependent patients, butorphanol cannot be substituted for opiate agonists after physical dependence has been established without prior detoxification. Butorphanol is probably not an effective antidote in the treatment of cardiovascular, respiratory, or behavioral depression induced by opiate agonists because of its relatively weak antagonistic effects.

Cautions

■ Adverse Effects

Incidence and type of adverse effects of butorphanol tartrate (administered parenterally or intranasally) are similar to those of opiate analgesics. Sedation is the most frequent adverse reaction and occurs in about 43% of patients receiving butorphanol; sedation occurs more frequently with butorphanol than with morphine, meperidine, or pentazocine. Dizziness occurs in about 19% and nausea and/or vomiting has been reported in 13% of patients receiving butorphanol tartrate. Clamminess, sweatiness, headache, vertigo, floating feeling, asthenia, anxiety, euphoria, nervousness, paresthesia, lethargy, confusion, and lightheadedness occur in 1–10% of patients. Other adverse CNS effects, such as unusual dreams, agitation, hallucinations, seizures, hostility, transient difficulty in speaking and/or executing purposeful movements, and delusion occur in less than 1% of patients receiving butorphanol. In equianalgesic dosage, adverse psychotomimetic effects such as hallucinations, dysphoria, unreality, depersonalization, and nervousness may occur more frequently with butorphanol than with morphine or nalbuphine. Insomnia has been reported in 11% of patients receiving butorphanol tartrate nasal solution. In addition, taste perversion, anorexia, constipation, and tinnitus occurred in 3–9% and otic pain and tremor were reported in 1% or more of patients receiving butorphanol tartrate nasal solution.

Other adverse GI effects, including vomiting, abdominal cramps, and constipation, occur in less than 1% of patients receiving butorphanol. Adverse cardiovascular effects include vasodilation and palpitation which occur in 1–9% of patients receiving the drug and chest pain, tachycardia, bradycardia and increased or decreased blood pressure which occur in less than 1% of patients. Hypotension associated with syncope (usually occurring within the first hour of administration) has been reported rarely in patients receiving butorphanol tartrate nasal solution, particularly in those who experienced similar adverse effects when receiving an opiate analgesic. Adverse dermatologic effects, such as rash or urticaria and itching, and other adverse effects, such as flushing and warmth, miosis, dry mouth, acrocyanosis, impaired urination, sensitivity to cold, tingling, diplopia, and blurred vision, also occur in less than 1% of patients receiving the drug. In addition, burning at the site of IV injection has been reported in patients receiving butorphanol tartrate injection.

Respiratory depression (decreased rate and depth of respiration) and apnea have occurred in less than 1% of patients receiving butorphanol; respiratory depression occurs mainly in patients receiving other drugs with CNS effects and in those with a history of CNS disease or respiratory impairment. In doses above the usual therapeutic range, butorphanol causes less respiratory depression than does morphine. Butorphanol-induced respiratory depression can be reversed by naloxone. The most common respiratory effects associated with the administration of butorphanol tartrate nasal solution are nasal congestion, which has been reported in 13% of patients, and dyspnea, epistaxis, nasal irritation, pharyngitis, rhinitis, sinus congestion, or upper respiratory infection, occurring in 3–9% of patients. Bronchitis, cough, and sinusitis have been reported in 1% or more of patients receiving butorphanol tartrate nasal solution.

■ Precautions and Contraindications

Because of possible adverse CNS effects such as drowsiness and dizziness, ambulatory patients receiving butorphanol should be cautioned against performing hazardous tasks requiring mental alertness or physical coordination such as driving a motor vehicle or operating machinery and warned about possible additive effects with other drugs that cause CNS depression. (See Drug Interactions: CNS Depressants.) Although butorphanol appears to have a low physical dependence liability (see Chronic Toxicity), the drug should be used cautiously in patients who are emotionally unstable or have a history of opiate abuse, and these patients should be closely supervised during long-term butorphanol therapy.

Butorphanol should be administered with caution and in low doses in patients with impaired respiration caused by other drugs, uremia, severe infection, severely limited respiratory reserve, bronchial asthma, respiratory obstruction, or cyanosis. In patients with acute myocardial infarction, ventricular dysfunction, or coronary insufficiency, butorphanol should be used only if the potential benefits justify the possible risks. Since butorphanol may slightly increase blood pressure, the drug should be used cautiously before surgery or anesthesia in hypertensive patients. If hypertension occurs, butorphanol should be discontinued and a hypotensive agent administered as necessary; butorphanol-induced hypertension reportedly has been managed with naloxone in patients who were not opiate dependent. In addition, since hypotension associated with syncope has been reported rarely in patients receiving butorphanol tartrate nasal solution, the manufacturer states that patients should be cautioned against performing activities that may pose risks if hypotension were to occur. Safe use of butorphanol in patients about to undergo biliary tract surgery has not been established, and the drug should be used with caution in these patients. Because butorphanol potentially may be associated with carbon dioxide retention and secondary elevation of CSF pressure, drug-induced miosis, and alterations in mental state (that may interfere with evaluation of CNS function), the drug should be used in patients with head injury only if the potential benefits justify the possible risks. In patients with head injury, the drug may also interfere with evaluation of CNS function.

Because it may be difficult to assess addiction in patients who have recently received substantial amounts of opiate agonists, butorphanol should be used with caution in these patients. The drug should be used in opiate-dependent patients only after they have been detoxified since butorphanol does not suppress the abstinence syndrome in these patients, and high doses may precipitate withdrawal symptoms as a result of opiate antagonist effect. Butorphanol should be used with caution in patients with renal or hepatic dysfunction. The drug is contraindicated in patients with known hypersensitivity to butorphanol or to benzethonium chloride contained in the multiple-dose vials of the injection or in the nasal solution of the drug.

■ Pediatric Precautions

Safety and efficacy of butorphanol in children younger than 18 years of age have not been established.

■ Geriatric Precautions

Since clearance is decreased and elimination half-life of butorphanol may be increased in patients older than 65 years of age, dosage and dosage interval of butorphanol tartrate should be modified in such patients. (See Dosage in Renal and Hepatic Impairment and in Geriatric Patients, in Dosage.) In addition, geriatric patients may be more sensitive to drug-induced adverse effects than younger individuals. Results of a long-term clinical study indicate that geriatric patients may tolerate dizziness associated with intranasal butorphanol tartrate less well than younger patients.

■ Pregnancy, Fertility, and Lactation

Safe use of butorphanol during pregnancy (except during labor) has not been established. Reproduction studies in rats, mice, and rabbits using butorphanol dosages of approximately 2.5–5 times the usual human dosage, during organogenesis, have not revealed evidence of harm to the fetus. However, subcutaneous butorphanol doses of 1 mg/kg were associated with higher incidences of stillbirths in rats. In addition, increased postimplantation losses occurred in rabbits receiving oral butorphanol doses of 30 and 60 mg/kg. There are no adequate and controlled studies to date using butorphanol tartrate in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risk to the fetus. When butorphanol is administered during labor and delivery, respiratory depression may occur in the neonate; the drug should be used with caution in women delivering premature infants. In one clinical study using 1-mg IV doses of butorphanol tartrate during labor, transient (10–90 minutes) sinusoidal fetal heart rate patterns were reported; however, no adverse neonatal outcomes occurred. Butorphanol should be used with caution in the presence of abnormal fetal heart rate pattern. Because of the absence of clinical experience with butorphanol nasal solution during labor and delivery, use of the nasal preparation is not recommended in such circumstances.

Reproduction studies in rats using oral butorphanol dosages of 160 mg/kg daily revealed a decreased pregnancy rate; however, this effect was not observed in rats using subcutaneous butorphanol dosages of 2.5 mg/kg daily.

Butorphanol is distributed into human milk following parenteral administration of the drug in nursing women. The manufacturer states that the amount of the drug distributed into milk probably is clinically insignificant, estimated at 4 µg/L of milk in a woman receiving 2 mg of butorphanol IM 4 times daily. Although there is no clinical experience with the use of butorphanol tartrate nasal solution in nursing women, it is assumed that the amount of the drug distributed into milk will be similar to that when administered parenterally.

Chronic Toxicity

Tolerance and psychological and physical dependence may occur in patients receiving butorphanol, and unnecessary increases in dosage or frequency of administration should be avoided. Studies in animals and in a small number

of human ve suggested that butorphanol may have a lesser dependence liability than opiate agonists such as morphine; the potential for abuse is reportedly less than that of codeine or propoxyphene. Although cases of butorphanol abuse and/or dependence have been reported, the relative dependence liability and abuse potential of butorphanol currently appears to be low to moderate. Butorphanol has been misused in combination with diphenhydramine by drug abusers in a manner similar to the parenteral use of pentazocine and tripelennamine (known as T's and blues), since the combination's effects are purported to be similar to those of IV heroin (diacetylmorphine).

Following abrupt discontinuance after prolonged use of butorphanol, withdrawal symptoms, which are similar to but more intense than those produced by pentazocine, have occurred and may include nausea, vomiting, abdominal cramping, diarrhea, increased temperature, diaphoresis, mydriasis, weight loss, restlessness, malaise, myalgia, rhinorrhea, increased blood pressure, itching, tachycardia, and "electric shocks" usually associated with a feeling of faintness. Acute withdrawal has been reported to develop within 4–24 hours after discontinuance of the drug in individuals who are dependent. Clonidine hydrochloride has been used in the management of acute butorphanol withdrawal in at least one individual.

Acute Toxicity

No instances of butorphanol overdosage have been reported, but expected symptoms would be respiratory depression, cardiovascular effects, and other CNS effects. Treatment consists of immediate IV administration of naloxone. Respiratory and cardiac status should be constantly evaluated, and appropriate supportive measures such as administration of oxygen, IV fluids and vasopressors, and assisted or controlled respiration should also be used if necessary.

Drug Interactions

■ CNS Depressants

The effects of butorphanol are additive with those of other CNS depressants such as general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, antihistamines, or alcohol. When butorphanol is used concomitantly with other depressant drugs, caution should be observed to avoid overdosage by using the smallest effective dose and reducing the frequency of dosing as much as possible. No information is available on the concomitant use of butorphanol with monoamine oxidase (MAO) inhibitors.

■ Other Drugs

Concomitant administration of butorphanol and pancuronium reportedly may cause an increase in conjunctival changes. In patients receiving a nasal vasoconstrictor (e.g., oxymetazoline), the rate of absorption of intranasal butorphanol may be decreased while the extent of absorption appears to be unchanged; therefore, a slower onset of analgesic action may occur in patients receiving butorphanol nasal solution immedicately following or concomitantly with oxymetazoline.

Since it is not known if drugs that affect hepatic microsomal enzymes (e.g., cimetidine, erythromycin, theophylline) may interfere with the metabolism of butorphanol, the manufacturer suggests that clinicians consider decreasing doses and increasing intervals between doses of butorphanol in patients receiving such drugs.

Dosage and Administration

■ Administration

Butorphanol tartrate is administered by IM or IV injection or by nasal inhalation using a spray pump. The nasal solution spray pump containing butorphanol tartrate should be assembled according to the manufacturer's instructions. Prior to initial use, the spray pump should be fully primed; priming of the pump should be repeated whenever the pump has not been used for 48 hours or longer. The patient instructions provided by the manufacturer should be consulted for use of the nasal solution spray pump. Since butorphanol nasal solution spray pump is an open delivery system that may increase environmental exposure of health-care personnel and visitors, the pump spray should be aimed away from such individuals.

■ Dosage

Dosage of butorphanol tartrate should be adjusted according to the severity of pain, physical status of the patient, and other drugs that the patient is receiving. (See Cautions: Precautions and Contraindications and Drug Interactions.)

The usual adult dose of butorphanol tartrate is 2 mg IM or 1 mg IV. These doses may be repeated every 3–4 hours as necessary. If repriming of the pump is necessary because of intermittent use, the spray pump will deliver about 8–10 metered doses, depending on the extent of repriming. The usual effective dosage, depending on the severity of the pain, ranges from 1–4 mg IM or 0.5–2 mg IV, repeated every 3–4 hours. There are insufficient clinical data to recommend IM doses greater than 4 mg.

After initial priming, the nasal solution spray pump delivers about 14–15 metered doses containing 1 mg of butorphanol tartrate per spray. If repriming of the pump is necessary because of intermitent use, the spray pump will deliver about 8-10 metered doses, depending on the extent of repriming. The usual initial intranasal butorphanol tartrate dose is 1 mg (1 spray in one nostril); if adequate analgesia is not achieved, an additional 1-mg dose may be given within 60–90 minutes. This initial dose sequence may be repeated in 3–4 hours if needed. For the management of severe pain, an initial dose of 2 mg (1 spray in each nostril) may be given to patients who can remain recumbent if drowsiness or dizziness occurs; however, these patients should not receive additional 2-mg doses at intervals shorter than 3–4 hours, since the incidence of adverse effects may be increased.

In the treatment of postepisiotomy and musculoskeletal pain, 4–16 mg of butorphanol tartrate has been given orally† every 4–6 hours.

■ Dosage in Hepatic or Renal Impairment and in Geriatric Patients

Patients with hepatic or renal impairment and geriatric patients should receive half of the recommended parenteral adult dose (i.e., 1 mg IM or 0.5 mg IV). If needed these doses may be repeated within usually not less than 6 hours. The usual initial dose of butorphanol tartrate nasal solution is 1 mg (1 spray in one nostril) in these patients; an additional 1-mg dose may be given within 90–120 minutes. This initial dose sequence may be repeated within usually not less than 6 hours.

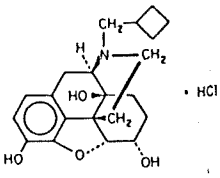
Preparations

Butorphanol Tartrate

Nasal Solution	1 mg/metered spray (10 mg/mL)	Stadol® NS®, Bristol-Myers Squibb (also promoted by Cephalon)
Parenteral Injection	1 mg/mL	Stadol®, Apothecon
	2 mg/mL	Stadol®, Apothecon

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Nalbuphine Hydrochloride



Chemistry and Stability

■ Chemistry

Nalbuphine hydrochloride is a synthetic partial opiate agonist analgesic. The drug is structurally related to naloxone and oxymorphone but pharmacologically similar to pentazocine and butorphanol.

Nalbuphine hydrochloride occurs as a white to slightly off-white powder and is soluble in water and slightly soluble in alcohol. The drug has pK_a values of 8.71 and 9.96. Nalbuphine hydrochloride injection is a sterile, nonpyrogenic solution of the drug in water for injection; the injection also contains citric acid and sodium citrate and may also contain parabens, sodium chloride, and sodium metabisulfite. The pH of nalbuphine hydrochloride injection is adjusted to 3.5 with hydrochloric acid and/or sodium hydroxide as necessary.

■ Stability

Nalbuphine hydrochloride injection should be protected from light and stored at 15–30°C. Commercially available single-dose containers of nalbuphine hydrochloride contain no preservatives and unused portions should be discarded.

Nalbuphine hydrochloride is reportedly physically compatible with some drugs (e.g., atropine sulfate, diphenhydramine hydrochloride, droperidol, glycopyrrolate, hydroxyzine hydrochloride, prochlorperazine, scopolamine hydrobromide) and with 5% dextrose, lactated Ringer's, and 0.9% sodium chloride

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Adult Dosage

In minor but painful general surgical procedures requiring endotracheal intubation and assisted or controlled respiration in adults, an initial sufentanil dose of 1–2 µg/kg is administered IV in conjunction with nitrous oxide and oxygen; additional IV doses of 10–25 µg may be given as necessary when movement and/or changes in vital signs indicate surgical stress or lightening of anesthesia. In more complicated, major surgical procedures in adults, an initial total sufentanil dose of 2–8 µg/kg is administered IV in conjunction with nitrous oxide and oxygen; additional IV doses of 25–50 µg may be given as necessary as determined by changes in vital signs that indicate surgical stress or lightening of anesthesia.

To provide general anesthesia without additional anesthetic agents when attenuation of the response to surgical stress is especially important, an initial sufentanil dose of 8–30 µg/kg is administered IV to adults in conjunction with oxygen and a skeletal muscle relaxant; additional IV doses of 25–50 µg may be given as necessary as determined by changes in vital signs that indicate surgical stress and lightening of anesthesia. Initial IV doses of 8–25 µg/kg generally attenuate catecholamine release and those of 25–30 µg/kg generally block sympathetic responses including catecholamine release during surgery but not during cardiopulmonary bypass. Initial IV doses of 8–30 µg/kg and supplemental doses of 25–50 µg are used in adults undergoing major surgical procedures such as cardiovascular surgery or neurosurgery performed with the patient in the sitting position when maintenance of favorable myocardial and cerebral oxygen consumption is preferred. Sufentanil has also been administered by intermittent IV infusion† as the primary anesthetic agent for the induction and maintenance of anesthesia in conjunction with 100% oxygen and a skeletal muscle relaxant. Following administration of preanesthetic medications, oxygen, and pancuronium bromide (0.01–0.02 mg/kg) in adults undergoing surgical procedures for coronary artery bypass grafting, sufentanil was infused at a rate of 300 µg/minute until unconsciousness developed up to a total dose of 3.8–4.9 µg/kg; following administration of a second dose of a skeletal muscle relaxant (e.g., succinylcholine) and intubation in these patients, sufentanil was infused over 30 minutes in a dose equivalent to that which previously produced unconsciousness. The surgical procedure was started and additional 50-µg doses of sufentanil were administered by IV injection as necessary as determined by systolic blood pressure response; at the end of the surgical procedure, the total dose of sufentanil for the entire procedure ranged from 11.1–15 µg/kg in adults.

Pediatric Dosage

The manufacturer states that when sufentanil is used to provide induction and maintenance of anesthesia without additional anesthetic agents in children younger than 12 years of age undergoing cardiovascular surgery, an initial anesthetic dose of 10–25 µg/kg is administered IV in conjunction with 100% oxygen and a skeletal muscle relaxant; additional IV doses of up to 25–50 µg each (total dose of up to 1–2 µg/kg) are recommended as necessary based on response to the initial dose and as determined by changes in vital signs that indicate surgical stress or lightening of anesthesia. Dosage in children younger than 2 years of age has not been established. (See Cautions: Pediatric Precautions.) Some clinicians report use of total sufentanil doses of 5–10 µg/kg infused at a rate of 1 µg/kg per minute in infants with mean ages of about 8–9 months undergoing repair of complex congenital heart defects†.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, chronic toxicity, acute toxicity, drug interactions, and dosage and administration of sufentanil citrate, see the Opiate Agonists General Statement 28:08.08.

Preparations

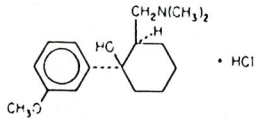
Sufentanil citrate is subject to control under the Federal Controlled Substances Act of 1970 as a schedule II (C-II) drug.

Sufentanil Citrate

Parenteral		
Injection	50 µg (of sufentanil) per mL	Sufenta® (C-II; preservative-free), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration.

Tramadol Hydrochloride



Description

Tramadol hydrochloride is a synthetic, centrally active analgesic. The drug (and its active M1 metabolite) acts as an opiate agonist, apparently by selective activity at the µ-receptor. In addition to opiate agonist activity, tramadol inhibits reuptake of certain monoamines (norepinephrine, serotonin), which appears to contribute to the drug's analgesic effect. Although the relative contribution of tramadol versus its M1 metabolite to analgesia in humans is unknown, the metabolite is 6 times more potent than the parent drug in producing analgesia in animal models and 200 times more potent in µ-receptor binding. The antinociceptic effect of tramadol is antagonized only partially by naloxone in some tests in animals and healthy individuals.

Although the pharmacologic effects of tramadol result in part from agonist activity at opiate receptors, the drug is not an opium derivative nor a semisynthetic derivative of morphine or thebaine. However, because tramadol is an agonist of *true* opiate receptors, not opiate-*like* (i.e., opi-*oid*) receptors, the drug is classified as an opiate agonist in the AHFS Pharmacologic-Therapeutic Classification©. (See Chemistry in the Opiate Agonists General Statement 28:08.08.)

Because of the drug's opiate agonist activity at µ-receptors, tramadol also can produce dependence; however, its abuse potential appears to be low, and tramadol is ***not*** subject to control under the Federal Controlled Substances Act of 1970 as a scheduled drug. Tolerance and manifestations of withdrawal also can occur, although such effects are relatively mild compared with those of other opiate agonists.

Tramadol shares many of the other pharmacologic and toxicologic effects of opiate agonists, including dizziness, somnolence, nausea, constipation, dry mouth, sweating, and pruritus. The respiratory depressant effects of the drug are less than those of morphine, and usually are not clinically important at usual oral doses. At relatively high doses (e.g., those administered parenterally), tramadol can produce respiratory depression, and even usual oral doses should be employed cautiously in patients at risk for respiratory depression. At usual oral doses, the drug exhibits minimal cardiovascular effects, although hypotension, syncope, and tachycardia can occur occasionally.

Uses

Tramadol hydrochloride is used orally as an analgesic for the relief of moderate to moderately severe pain. Comparative and noncomparative clinical studies have shown that tramadol is an effective analgesic agent in the treatment of moderately severe acute or chronic pain, including postoperative, gynecologic, and obstetric pain, as well as pain of various other origins, including cancer.

Single oral doses of tramadol hydrochloride ranging from 50–200 mg have provided relief of postoperative pain in patients who have undergone various types of surgery, including orthopedic, gynecologic, and cesarean section, and in oral surgical procedures (e.g., extraction of impacted molars). In controlled clinical studies of postoperative pain, tramadol hydrochloride administered as a single oral dose of 150 mg was comparable to, or more effective than, the combination of acetaminophen 650 mg and propoxyphene napsylate 100 mg. In patients undergoing oral surgery, a single oral tramadol hydrochloride dose of 50 or 75 mg provided analgesia in some patients, and a single oral dose of 100 mg provided analgesia that was superior to that provided by 60 mg of codeine sulfate but inferior to the combination of codeine phosphate 60 mg and aspirin 650 mg. In a study of patients undergoing dental extraction, a single oral dose of tramadol hydrochloride 75 or 150 mg was more effective than codeine phosphate 60 mg, and tramadol hydrochloride 150 mg was more effective (while tramadol hydrochloride 75 mg was less effective) than acetaminophen 650 mg and propoxyphene napsylate 100 mg.

In several long-term controlled clinical studies of patients with chronic pain (e.g., low back pain, cancer pain, neuropathic pain, pain associated with orthopedic and joint disorders), tramadol hydrochloride dosages averaging 250 mg daily administered in divided doses were as effective as acetaminophen 300 mg or aspirin 325 mg administered with codeine phosphate 30 mg 5 times daily or acetaminophen 500 mg administered with oxycodone hydrochloride 5 mg 2 or 3 times daily. Tramadol also may be useful in the management of cancer pain when nonopiate-agonist analgesics are no longer effective (i.e., step 2 of the WHO guidelines for cancer pain treatment). In a study of cancer patients with severe chronic pain, tramadol provided effective analgesia but was less effective than an extended-release morphine dosage form; however,

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patients receiving tramadol experienced only mild adverse effects, none of which resulted in patient withdrawal from the study, while about 23% of patients receiving extended-release morphine withdrew from the study because of severe adverse effects.

The onset and peak of analgesia occurs within 1 and 2–4 hours, respectively, after oral administration of tramadol hydrochloride; peak plasma concentrations are achieved about 2 hours after oral administration, corresponding to the time of peak analgesic effect. The duration of analgesia produced by a single oral dose of tramadol hydrochloride has been reported to be about 3–6 hours.

The manufacturer cautions that tramadol is not recommended for use in patients dependent on opiate agonists. Patients with a recent history of having received substantial amounts of opiate agonists may experience manifestations of withdrawal if tramadol is initiated. Because of the difficulty in assessing dependence in such patients, tramadol should be used with caution in patients with such a history.

Administration of tramadol may cause effects similar to those produced by other opiate agonist drugs, and many of the usual precautions of opiate agonist therapy should be observed. (See Description and the manufacturer's labeling.) Manifestations of overdosage also are similar to other opiate agonists, although some (e.g., seizures) may not be reversible with an opiate antagonist (e.g., naloxone). In animals, naloxone actually increased the seizure risk of tramadol. For additional information about overdosage of opiate agonists, see Acute Toxicity in the Opiate Agonists General Statement 28:08.08.

Seizures have occurred during tramadol therapy, and the manufacturer warns that the drug may enhance the risk of seizures in patients receiving monoamine oxidase (MAO) inhibitors, antipsychotic agents, or other drugs that decrease the seizure threshold and in those with an underlying seizure disorder or who are otherwise at increased risk of seizures. The manufacturer also warns that tramadol decreases the synaptic reuptake of the monoamine neurotransmitters norepinephrine and serotonin; therefore, the drug should be used with great caution in patients receiving MAO inhibitors. Because tramadol may potentiate the effects of other CNS depressants (e.g., alcohol, sedatives and hypnotics, other centrally acting analgesics, opiate agonists), the drug should be used with caution, and dosage of tramadol may need to be decreased, in patients receiving such drugs; tramadol should not be used in patients who are acutely intoxicated with other CNS depressants.

For a more complete discussion of the usual precautions associated with opiate agonist therapy, see the Opiate Agonists General Statement 28:08.08.

Dosage and Administration

■ Administration

Tramadol hydrochloride is administered orally. Since food does not affect substantially the rate or extent of absorption of tramadol hydrochloride, the manufacturer states that the drug can be taken without regard to food.

■ Dosage

The manufacturer states that safety and efficacy of tramadol hydrochloride in children younger than 16 years of age have not been established.

The usual initial oral dose of tramadol hydrochloride in adults and children 16 years of age and older with moderate or with moderately severe pain is 50 or 100 mg, respectively. For continued relief, 50–100 mg can be administered every 4–6 hours as needed. Dosages exceeding 400 mg daily generally are not recommended by the manufacturer. However, patients receiving chronic carbamazepine therapy (up to 800 mg daily) may require tramadol hydrochloride dosages up to twice usual.

While the usual oral tramadol hydrochloride dosage of 50–100 mg every 4–6 hours as needed can be used in geriatric patients 65 years of age and older with normal renal and hepatic function, the manufacturer recommends that dosage not exceed 300 mg daily in those older than 75 years of age.

■ Dosage in Renal and Hepatic Impairment

Dosage of tramadol hydrochloride should be reduced in certain patients with renal or hepatic impairment by decreasing the frequency of administration.

Adults and children 16 years of age and older with creatinine clearances less than 30 mL/minute may receive an oral tramadol hydrochloride dosage of 50–100 mg every 12 hours, not to exceed 200 mg daily. Since less than 10% of a dose of tramadol hydrochloride is removed by hemodialysis, patients undergoing dialysis may receive their usual dosage on the day of dialysis.

Adults and children 16 years of age and older with hepatic cirrhosis may receive a tramadol hydrochloride dosage of 50 mg every 12 hours.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications.

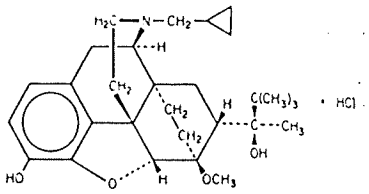
Preparations

Tramadol Hydrochloride

Oral		
Tablets, film-coated	50 mg	Ultram®, Ortho-McNeil

OPIATE PARTIAL AGONISTS 28:08.12

Buprenorphine Hydrochloride



Chemistry and Stability

■ Chemistry

Buprenorphine hydrochloride is a synthetic opiate partial agonist analgesic. Buprenorphine is derived from thebaine and is structurally related to morphine but pharmacologically similar to other currently available opiate partial agonists. Buprenorphine differs structurally from morphine in that buprenorphine contains a carbon bridge on the C ring; in addition, the methyl group on the nitrogen atom of morphine is replaced by a cyclopropylmethyl group, the C-6 position is substituted with a methoxy group rather than a hydroxyl group, the C-7 position is substituted with an alkylhydroxyl group, and there is a single rather than a double bond between C-7 and -8.

Buprenorphine hydrochloride occurs as a white, crystalline powder and has solubilities of 17 mg/mL in water (pH 4.4) at 25°C and 42 mg/mL in alcohol at room temperature. The drug has pK_as of 8.24–8.42 (amine) and 9.92–10 (phenol). Commercially available buprenorphine hydrochloride injection is a sterile solution of the drug in 5% dextrose injection. The injection occurs as a clear solution and has an osmolality of 297 mOsm/kg. The pH of the injection is adjusted to 3.5–5.5 with hydrochloric acid.

Potency of buprenorphine hydrochloride is expressed in terms of buprenorphine. Each mL of commercially available buprenorphine hydrochloride injection contains 0.324 mg of buprenorphine hydrochloride, equivalent to 0.3 mg of buprenorphine.

■ Stability

Buprenorphine hydrochloride injection should be protected from prolonged exposure to light and stored at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided. Buprenorphine hydrochloride injection has an expiration date of 2 years following the date of manufacture.

Buprenorphine hydrochloride is stable in solution at a pH of 3.5–5.5. The drug may undergo substantial decomposition when autoclaved. When mixed in a 1:1 volume ratio, buprenorphine hydrochloride injection reportedly is physically and chemically compatible with atropine sulfate, diphenhydramine hydrochloride, droperidol, glycopyrrolate, haloperidol lactate, hydroxyzine hydrochloride, promethazine hydrochloride, scopolamine hydrobromide, 5% dextrose, 5% dextrose and 0.9% sodium chloride, lactated Ringer's, and 0.9% sodium chloride injections but incompatible with diazepam and lorazepam injections. Compatibility depends on several factors (e.g., the concentrations of the drugs, specific diluents used, resulting pH, temperature). Specialized references should be consulted for specific compatibility information.

Pharmacology

■ Opiate Agonist and Antagonist Properties

Buprenorphine hydrochloride is an opiate partial agonist and shares many of the actions of opiate agonists. The drug exhibits analgesic and opiate antagonist activities. Buprenorphine is thought to act as a partial agonist at μ-opiate receptors in the CNS and peripheral tissues. The activity of the drug at κ- and δ-opiate receptors is less well defined. Several studies suggest that buprenorphine acts as an agonist at κ-opiate receptors, but some evidence suggests that the drug has antagonist activity at these receptors in peripheral

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TRAMADOL DUR PROFILE REVIEW

(Presented at the January 8, 1997 DUR Board Meeting)

Points of significance:

- ❒ Cases analyzed were from Medicaid Beneficiary Paid Claim Profiles
- ❒ Review dates involved paid claims from May 1995 through October 1996
- ❒ Cases were randomly selected by the DUR Retrospective Program administered by the Kansas Pharmacy Foundation
- ❒ Dosage criteria consisted of the maximum daily dose per FDA guidelines: 1-2 tablets every 4-6 hours as needed-not to exceed 400mg (8 tablets) per day
- ❒ Concomitant drug utilization involving any combination of an NSAID, narcotic analgesic, or muscle relaxant

Results:

- ⇨ 42 cases were reviewed
- ⇨ 10/42 cases (24%) were deemed within appropriate utilization criteria
- ⇨ 32/42 cases (76%) fell outside of the appropriate utilization criteria
  of those 32 cases the following dosage results were obtained:
  - ⇨ 11/32 cases averaged between 8-9 tablets/day
  - ⇨ 19/32 cases averaged between 10-17 tablets/day
  - ⇨ 1/32 cases averaged 27 tablets/day
  - ⇨ 1/32 cases averaged 35 tablets/day
- ⇨ Concomitant NSAID usage appeared in 21/32 outlier cases
  Concomitant NSAID usage appeared in 5/10 cases deemed as appropriate use
- ⇨ Concomitant narcotic analgesic usage appeared in 23/32 outlier cases
  Concomitant narcotic analgesic usage appeared in 10/10 cases deemed appropriate use
- ⇨ Concomitant muscle relaxant usage appeared in 11/32 outlier cases
  Concomitant muscle relaxant usage appeared in 4/10 cases deemed as appropriate use
- ⇨ Concomitant usage involving all three areas appeared in 6/32 outlier cases
  Concomitant usage involving all three areas appeared in 2/10 cases deemed appropriate
  of those 32 outlier cases the following was also observed:
- ⇨ Age data varied between 27- 62 years old ; average age of 39 years old
- ⇨ Sex data results Males = 25% Females= 75%
  of all 42 cases reviewed the following Kansas counties were involved:

⇨ Sedgwick (16 cases)	Coffey	Labette
Montgomery (3 cases)	Cowley	Linn
Wyandotte (2 cases)	Crawford	Butler
Douglas	Ford	Sumner
Kingman	Norton	
Reno	Shawnee	

- ⇨ There was a healthcare provider trend noted in Sedgwick County

Kansas DUR Bulletin
DRUG UTILIZATION REVIEW
December 1996 Volume18, Number 4

Focus on Tramadol (Ultram®)

By: Lawrence W. Davidow, R.Ph., Ph.D., and R.L. Legino, R.Ph.

Pain is one of the most common complaints which will prompt patients to see a physician. For example, in 1990 it was estimated that 37.9 million Americans (15% of the population) had an arthritic condition.[1] In addition, as much as 60-80% of the population is expected to experience low back pain at some point in their lives.[2] Traditionally, the physician has managed intractable chronic pain using strong opioids, while the management of less severe pain has primarily included nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are useful because they possess both analgesic and anti-inflammatory effects. However, there is an increasing appreciation that long-term use of NSAIDs can produce serious gastrointestinal side effects, especially in the elderly.[3]

Analgesics such as codeine (including acetaminophen with codeine), propoxyphene, hydrocodone, and meperidine are often used for moderate pain relief. However these agents possess the same adverse-effect profile as the true opioids, thus greatly limiting their use.

When tramadol (Ultram®) was released it appeared to have potency between NSAIDS and stronger opioids but an improved side effect profile. The drug was introduced as an analgesic that represented an advance in the management of moderate to moderately severe pain. Ultram® is neither a nonsteroidal anti-inflammatory drug (NSAID) nor a pure opioid. The mechanism by which tramadol produces analgesia differs from the opioids in that it possesses only a modest binding affinity for opioid receptors (predominantly the mu-opioid receptor) and also weakly inhibits neuronal norepinephrine (NE) and serotonin (5-HT) reuptake. Its dual activity is attributed to the fact that tramadol is a racemic mixture in which the (+)-enantiomer possess the opioid receptor activity whereas the (-)-enantiomer is responsible for inhibiting NE and 5-HT reuptake.[4] Because the activity of either enantiomer with its respective receptor is much lower than reference compounds (i.e. codeine at the opioid site and imipramine for NE reuptake) one hypothesis would suggest that the analgesic action of tramadol results from the synergistic interaction of both pharmacological properties.[5] It is this dual mode of action that makes Ultram® another choice for treatment of chronic pain.

TABLE 1
Incidence (%) of most frequently occurring adverse experiences reported during the first 7 days of therapy in two U.S. pain trials [11]

Adverse Effect	Tramadol	Acetamin/Codeine (300mg/30mg)	Aspirin /Codeine (325mg/30mg)
Dizziness	26	26	16
Nausea	24	29	35
Constipation	24	51	34
Headache	18	16	7
Somnolence	16	24	19
Vomiting	9	5	6

Tramadol's pharmacokinetic properties reveal that the drug is rapidly and almost completely absorbed following oral administrations with peak plasma concentrations occurring approximately two hours after ingestion[6]. Oral administration of tramadol HCl with food does not significantly affect its rate or extent of absorption.[7] Therefore, Ultram® can be administered without regard to food. The mean absolute bioavailability of oral tramadol is 75% with multiple dosing of Ultram® 100mg four times daily for 7 days, the bioavailability increased to > 90% indicating a saturation of first-pass metabolism[6] with a plasma elimination half-life of 6.7 hours.[8] To date 11 metabolites

Continued next page

been identified with approximately 90% of tramadol and its metabolites eliminated via renal excretion.[7]

Prior to its release in the United States, tramadol was evaluated for efficacy and safety in 25 randomized, placebo-controlled studies. Tramadol was found in these studies to be equally effective as many of the commonly used opioids, including codeine (Tylenol #3®)[9] and dextropropoxyphene (active enantiomer of propoxyphene).[10]

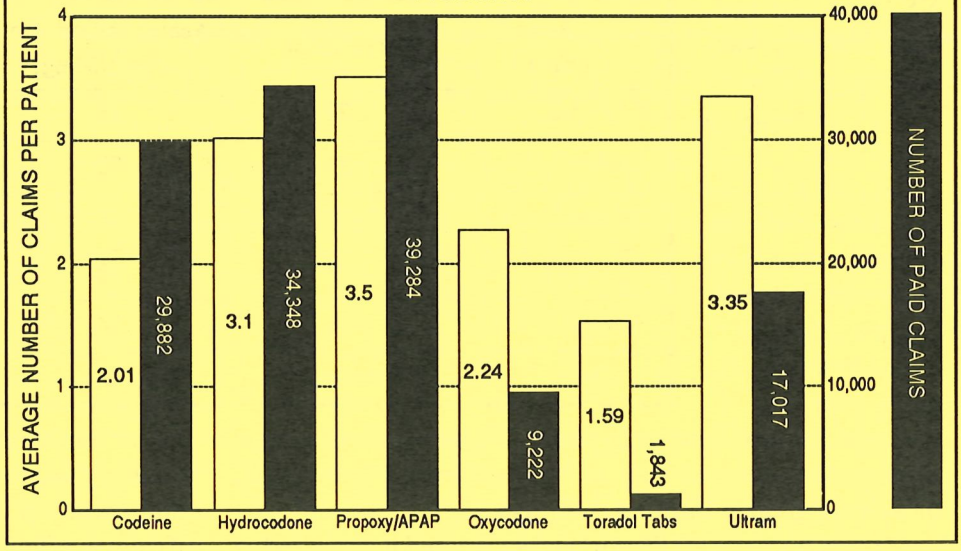
Tramadol's side effect profile is very nearly identical to that of the opioids. Table 1 illustrates the cumulative incidence of adverse effects occurring in 550 patients during the double-blind or open-label extension period in U.S. studies *(inset page 1)*.

This data may suggest that tramadol does not have significant advantage over opioid analgesics in regard to its side effect profile.

At present there are no published reports which compare tramadol to a NSAID currently available in the U.S. However, data on file at Ortho-McNeil show a randomized, double-blind, parallel study comparing the efficacy and safety of tramadol to ibuprofen in 293 patients with chronic hip or knee pain due to osteoarthritis.[12] Patients were required to be on a stable dose of a NSAID for 30 days prior to entering the study. Patients were allowed to titrate the dose of the study medication. The maximum dose of tramadol was 400 mg/day; the maximum dose of ibuprofen was 2400 mg/day. At the conclusion of the study the difference between treatment groups was deemed not statistically significant. Adverse events including nausea, constipation, drowsiness, vomiting, fatigue, weight/appetite loss was reported more frequently in the tramadol group. An increase in blood pressure was seen more frequently in the ibuprofen group. More patients in the tramadol group discontinued the study due to adverse effects (39% versus 9%). Nausea was the adverse effect that most frequently resulted in discontinuation of patients from the tramadol group. Ortho-McNeil has indicated that Ultram® does not inhibit the synthesis of prostaglandins and has not shown the serious adverse events (gastrointestinal ulcer formation, renal and hepatic dysfunction) generally associated with nonsteroidal anti-inflammatory drugs. However, more studies are needed before it can be determined which patients may benefit from switching to tramadol from a NSAID. The healthcare provider must weigh potential benefits (i.e. reduced risk for serious gastrointestinal injury) against potential risks (i.e. nausea, dizziness and drowsiness) on an individual basis.

Another area of important consideration for the healthcare provider involves drug interactions. Concomitant administration of tramadol and **cimetidine** has caused significant increases in the bioavailability and urinary excretion of tramadol. However, no dosage adjustments are recommended when cimetidine is routinely administered. Concomitant administrations of **quinidine** and tramadol resulted in increased concentration of tramadol, however clinical consequences have not been fully investigated. Compared with a placebo, administration of tramadol during **carbamazepine** therapy resulted as a decrease in bioavailability of tramadol. As such, patients receiving up to 800 mg of carbamazepine daily may require up to twice the dose of Ultram®. Finally, because Ultram® inhibits the uptake of norepinephrine and serotonin, it should be used with caution in patients taking **monoam-**

FIGURE A



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2-13

ine ... ase inhibitors because toxicity was increased in animal tests. Ultram® is contraindicated in cases of hypersensitivity to tramadol and in cases of acute intoxication involving alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs.[13]

Upon initial release the Food and Drug Administration did not subject tramadol to the Federal Controlled Substances Act as a scheduled drug. The low affinity of tramadol for the mu-opioid receptor was thought to reduce the likelihood that patients will experience euphoria, develop tolerance to the drug, or suffer withdrawal effects when the drug was discontinued.[14] However, ongoing safety surveillance conducted by Ortho-McNeil shows that tramadol may produce either drug-dependence or withdrawal. As a result of this abuse potential, tramadol is not recommended for use in patients who have a history of opioid abuse. Revised labeling for tramadol states "Ultram® has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids." In addition, recent safety surveillance information supplied by Ortho-McNeil indicates that seizures have been reported in patients receiving Ultram® in doses above the recommended range, as well as, within the recommended dosing range. Postmarking experience further suggests that seizures in patients taking Ultram® are rare and occur in patients with predisposing risk factors for seizures such as head trauma, metabolic disorder, alcohol and drug withdrawal, CNS infections or previous history of seizures or epilepsy. Ultram® may increase risk of seizure in patients taking tricyclic antidepressants or tricyclic compounds, selective serotonin reuptake inhibitors, MAO inhibitors, neuroleptics, or other drugs which lower seizure threshold. Such predisposing risk factors should be considered when prescribing Ultram®, as the seizuregenic mechanism has not be determined.[15]

CONCLUSION

The DUR Board has been monitoring the dispensing and utilization practices of tramadol within the Kansas Medicaid population.

Data collected from a retrospective review of Kansas Medicaid paid claims between July 1995 and June 1996 were analyzed.

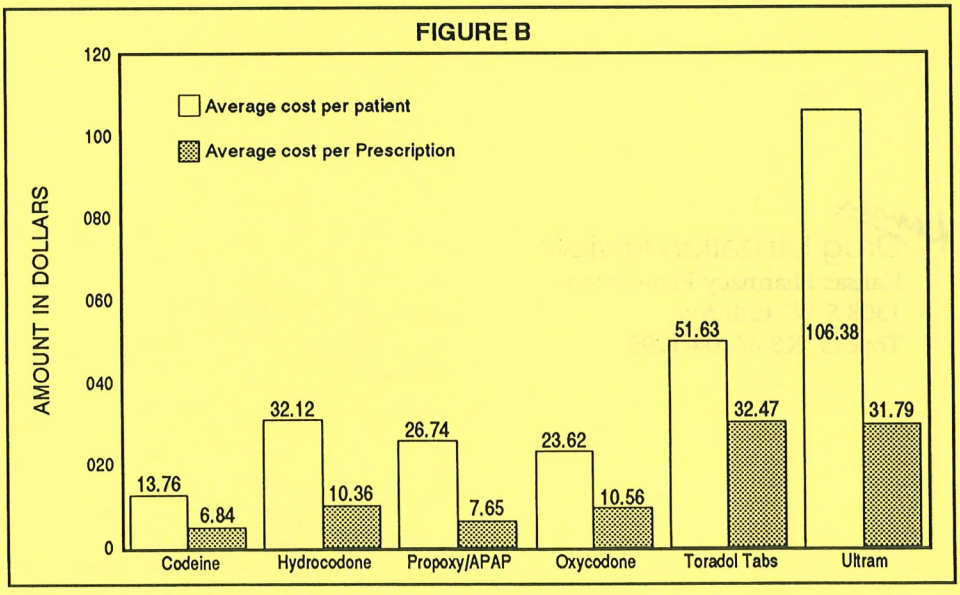
The first observation was determined from the number of paid claims for tramadol versus selected analgesic drug products and the average number of claims per patient (Figure A). These selected drugs consisted of products containing hydrocodo... deine, oxycodone, propoxyphene/acetamineophen, and ketorolac (Toradol®). In the darkened portion of the bar graph it can be noted that Ultram® utilization resulted in 17,017 paid claims compared to the more frequently prescribed propoxyphene/acetaminophen (Darvacet - N 100®)

However, when the average number of claims per patient is reviewed (lighter portion of Figure A bar graph) there is a dramatic increase noted with tramadol, nearly equal that of propoxyphene/acetaminophen. This would suggest that among those Medicaid consumers being prescribed Ultram®, utilization is high.

A second observation was determined from a comparison of drug costs (Figure B) arising from the amount of claims paid by the state of Kansas and the average cost to treat each patient. The data indicated that $540,948 was spent on 17,017 tramadol claims. This totals one third of the

Continued

FIGURE B



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nt paid out involving all of the selected drug products combined. It also represents a substantial cost difference compared to the 39,284 number of paid claims for propoxyphene/acetaminophen totalling $300,433.

The average cost of $31.79 per tramadol prescription was nearly 4.5 times the $6.84 per codeine prescription. As a result of this information the Board has determined that the current practice of prescribing large quantities of tramadol per each prescription has resulted in an average prescription cost of $106.38 per patient on tramadol.

An on-going DUR review of tramadol has led to concern about prescribing practices by Kansas Medicaid healthcare providers. As previously indicated, the intended clinical use of Ultram® is for those patients in need of long term analgesic therapy in whom NSAID or narcotic therapy may be inappropriate. In accordance with pharmaceutical drug recommendations, Ultram® should not be used in acute pain situations where alternative drug therapy is available and can be used without significant complications and at a lower cost. As such, the DUR Board has recommended to the Department of Social and Rehabilitation Services a limitation on dispensed quantities to no more than the maximum allowable therapeutic dosage. In addition, the DUR Board has recommended that educational strategies be employed to disseminate information to Kansas Medicaid health care providers on tramadol and pain management. ✧

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1997 KANSAS LEGISLATIVE SESSION
House Bill No. 2225

PHARMACY PRACTICE ACT

House Committee on Health and Human Services

Monday, February 17, 1997.

Mr. Chairman and members of the committee, my name is Larry Froelich and I serve as the executive secretary to the Board of Pharmacy. I appear before you today on behalf of the Board in support of **HB 2225**.

There are several requested changes of KSA 65-4111 entitled "Substances included in schedule IV". I would like to take this opportunity to explain what would be accomplished by changing this statute and increasing the controls on these drugs.

I want to explain briefly, the differences between over-the-counter and legend, as well as controlled and non-controlled substances. All drugs approved by the Food & Drug Administration (FDA) are classified into either non-prescription (or over-the-counter) or prescription (or legend). The terms prescription and legend are interchangeable. "Legend" comes from the wording on the products' label that states, Caution: Federal law prohibits dispensing without a prescription. The FDA has determined that the labels of these products cannot contain all the data sufficient for safe usage of these products by the consumer, therefore the FDA requires a prescription for

these drugs. We then have two classes of drugs, those approved by the FDA as non-prescription (or over-the-counter) medications OR those approved by the FDA as prescription (or legend) medications.

The prescription (or legend) medications can then be further defined as either controlled OR non-controlled substances. Controlled substances are then broken down into 5 schedules based on their tendency for abuse potential, whether it is physical, psychological, or both.

Classes of Controlled Substances are:

- Schedule **I** - These drugs have a high potential for abuse and no accepted medical use in the US. Examples: Heroin, LSD, Peyote
- Schedule **II** - These drugs have a high potential for abuse but do have a currently accepted medical use. Examples: Morphine, Cocaine, *Demerol, Percodan, Ritalin*
- Schedule **III** - These drugs have a lower potential for abuse than schedule II. Examples: *Doriden, Plegine, Tylenol #3*
- Schedule **IV** - These drugs have a low potential for abuse, which may lead to limited physical or psychological dependence. Examples: *Valium, Xanax, Darvocet*
- Schedule **V** - These drugs have the lowest abuse potential and may consist of over-the-counter preparations that might be sold without a prescription. Examples: *Novahistine-DH, Robitussin-AC, Lomotil*

I am asking you to move non-scheduled prescription drugs into a controlled substance category, specifically a schedule IV controlled substance classification. The FDA's current assessment of the public health risks offered by these products, is that abuse problems would best be managed by the States in their regulation of the practice of medicine and pharmacy. The Drug Enforcement Agency (DEA) continues to review these drugs, but movement is too slow towards increasing the controls.

The first change appears in section 1, subsection (b). This is on page 1, line 29. The Board of Pharmacy is requesting addition of Carisoprodol to this statute, thus changing the status of this medication from a non-controlled prescription product to a schedule IV controlled substance prescription product.

The second medication change to this statute is found in section 2, subsection (e). This is on page 3, line 21. The Board of Pharmacy is requesting the addition of Butorphanol to this statute, thus again changing this product to a schedule IV controlled substance prescription product.

The third medication change to this statute is found in section 2, subsection (e). This is on page 3, line 23. The Board of Pharmacy is requesting the addition of Tramadol to this statute, thus again changing this product to a schedule IV controlled substance prescription product.

Why control these medications and what are the problems ?

CARISOPRODOL: The brand name for this drug is *SOMA*, marketed by Wallace Labs. It is also available generically. Carisoprodol has an abuse potential due to its sedative effect leading to its pharmacological activity as a skeletal muscle relaxant. In addition, the drug is metabolized in the body to meprobamate, a commercially available anti-anxiety agent which is itself a schedule IV controlled substance. The similarity to morphine is especially notable in the overdose toxicity profile. It has been documented to have a psychological abuse potential especially in patients having a history of drug abuse.

BUTORPHANOL: The brand name for this drug is *STADOL*, marketed by Bristol-Myers Squibb, and is not available generically. The FDA and some states have noted reports of abuse of this drug since approval of the nasal spray dosage form on December 12, 1991. The Assistant Secretary for Health recommended that Butorphanol be scheduled in the Controlled Substances Act on September 30, 1996.

TRAMADOL: The brand name for this drug is *Ultram*, marketed by McNeil Pharmaceutical, and is not available generically. Initially the FDA considered this drug to have a low abuse potential, but ongoing safety studies conducted by Ortho-McNeil have found that Tramadol may indeed produce drug dependence or withdrawal symptoms upon discontinuation of the drug, especially in patients having a history of opioid abuse. Evidence suggestive of abuse may be found in the Kansas DUR bulletin which states that Medicaid claims for Ultram show "large quantities…per prescription" and high number of claims per patient almost equal to that for Darvocet-N 100, a schedule IV controlled drug.

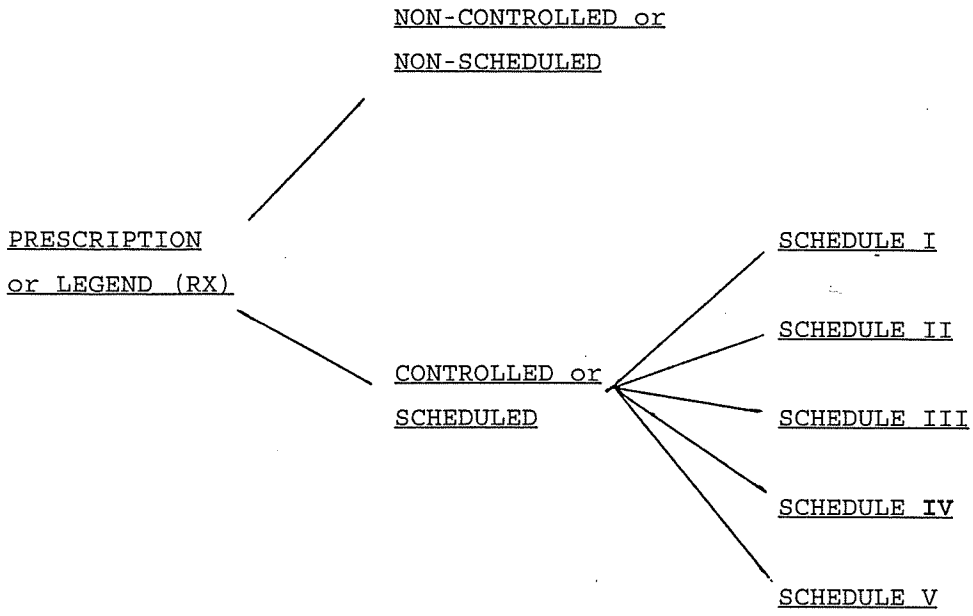
How will controlling these drugs solve the problem ?

A prescription for a schedule IV controlled substance can only be filled initially plus a maximum of 5 refills for a total of 6 fills. The number of fills currently allowed per prescription is unlimited, this will be cut to 6 fills per prescription. The pharmacist will have to check with the practitioner to obtain another prescription after 6 fillings. The current amount of time to fill these prescriptions is one year. For a schedule IV controlled substance, the maximum time permitted is 6 months after initial filling. The pharmacist will have to check with the practitioner to obtain another prescription after 6 months. This will help ensure that only patients who have a therapeutic need for the drug will continue to obtain this drug. Distribution of free samples of controlled substances is prohibited in Kansas. This was enacted through Board regulations to prevent diversion of controlled substance samples. Scheduling these medications would prohibit free sampling of these drugs. The pharmacist would be responsible for inventory control of these, along with other requirements for inventory of other controlled substances. If the pharmacist were upset about the additional inventory requirements for these products, they would be here opposing this legislation associated with scheduling these products, not here in support of this change. Physicians are not subject to more paperwork. They would be required to make a notation in the patient's chart when additional refills are added or new prescriptions given, but this might mean a note every six months in a patient's chart, as opposed to a yearly note. The physician would not be required to write new prescriptions for these medications, they may be telephoned into the pharmacy. Since the DEA does not currently have these drugs scheduled, the physician would not be under additional scrutiny from the Federal Government, but would be subject to scrutiny from Kansas agencies. Making these medications schedule IV controlled substances in Kansas will not adversely affect the health and welfare of the citizens of Kansas. It will call for closer scrutiny of drug therapy, since we are not limiting the quantity dispensed, nor limiting access to these medications, but rather asking that the need for therapy be reviewed more frequently.

The final change to this statute is found in section 1, subsection (d). This is on page 3, lines 12-15. This change involves striking language that the Board of Pharmacy found to be outdated. The original language suggests that DEA was studying the removal of this drug from the schedule IV substances. DEA is NOT reviewing, nor even considering reviewing this drug, therefore the language is no longer needed.

The Board of Pharmacy respectfully requests favorable passage out of committee of **HB-2225**. Thank you for allowing me to appear before you, and I am available for any questions.

OVER-THE-COUNTER (OTC)



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February 17, 1997

Chairman Mayans
Members of the Committee on Health and Human Services

RE: HB 2225

I am Carol Macdonald, Administrative Secretary for the Kansas Dental Board.

The Dental Board supports the Board of Pharmacy in their effort to add certain drugs to the list of controlled substances.

Of particular interest to the Board is the drug butorphanol, found on page 3, line 21. This is a drug with which a few of our licensees have had problems. One of our licensees voluntarily surrendered his license to practice dentistry rather than making an effort to cease using it.

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Statement of Brad Smoot
Legislative Counsel for Johnson & Johnson
House Health & Human Services Committee
Hearings on 1997 House Bill 2225
February 17, 1997

Johnson & Johnson (J&J) is a U.S. manufacturer and worldwide distributor of prescription pharmaceutical products and over-the-counter medications. Ortho McNeil is the wholly owned subsidiary corporation which markets tramadol under the brand name "Ultram." 1997 HB 2225 would add tramadol as a controlled substance pursuant to the Uniform Controlled Substances Act, K.S.A. 1996 Supp. 65-4101, *et seq.* See HB 2225, page 3, line 23. For a variety of reasons, we believe the scheduling of tramadol by the state of Kansas is neither warranted nor beneficial to patients and physicians. We appreciate this opportunity to express our opposition to this provision of HB 2225.

The Uniform Controlled Substances Act is used by the various states and the federal government to identify products of widespread abuse potential. Depending on which of the five schedules a product is placed, the laws impose distinct criminal penalties and legal limitations for possession, sale, distribution, labeling, reporting, dispensing and prescribing. These penalties and limitations impact patients, doctors, hospitals, wholesalers, law enforcement and federal and state oversight agencies. Of all the thousands of prescription-only drugs available under FDA approval, only a few dozen find their way onto the controlled substances schedules. J&J supports federal and state efforts to control abuse of prescription drugs. However, we do not believe tramadol, in only its second year of U.S. availability, deserves to be listed on Schedule IV as a "controlled substance."

To begin with, the Kansas Uniform Controlled Substances Act places responsibility for administration of the act on the state Board of Pharmacy. K.S.A. 1996 Supp. 65-4102 requires the Board to annually submit in writing a list of the products proposed for scheduling to the Speaker of House and the President of the Senate. The list is to be accompanied by the reasons for the proposed change

in the schedules and is to specifically include consideration of eight different criteria. A copy of the statute including the statutory obligation and criteria is attached for your convenience. I have contacted the offices of the Speaker and the President and have been advised that no such report has been submitted.

This statutory obligation of the Board is a matter of long standing and was unchanged by amendments to this section as recently as 1994. We can only presume that the Legislature meant what it said in the law and had some valuable purpose in mind by providing this detailed procedure prior to scheduling. From the standpoint of the public, patients, patient advocacy groups, physicians, pharmacists and even drug manufacturers, the required annual report would give all interested parties early warning of the Board's intentions, reasons and scientific evidence for scheduling a given product. Those who support or oppose the Board's proposed action might then be better able to provide information and opinion to the legislature. J&J has been aware of the Pharmacy Board's intention to seek scheduling of tramadol for several weeks but has not seen scientific data or detailed reasons for the proposed change until today. Patients and providers probably have had even less notice of this proposal and may have learned of it only when the bill was printed just over a week ago. May I suggest that these statutory requirements should not be ignored.

Tramadol is a prescription-only pain killer. It is particularly useful for physicians treating patients who have difficulties with older non-steroidal medicines like ibuprofen. Such patients may suffer stomach and intestinal bleeding which can, in 1% of such cases, lead to death. Tramadol has been available in Europe since 1977, is used in 70 countries and statistical data suggests that the incidence of patient abuse is small (1 to 1.5 per 100,000). Available in the U.S. since only 1995, Tramadol is a new weapon in the medical arsenal.

Tramadol was not placed on the controlled substances list when it was first introduced two years ago. The DEA has not placed it on the federal controlled substances list. The FDA has not recommended that it be controlled. No foreign country and no state has scheduled tramadol. If HB 2225 were to be enacted, Kansas would be the first to treat tramadol as a controlled substance. While being first is not necessarily bad, the lack of interest throughout the country and the world in doing what is proposed here should, at the very least, give us all pause to reflect on the proposal. The evidence suggests a low

level of tramadol abuse. Anecdotal reports of abuse are not widespread and are within acceptable and previously predicted limits. The facts simply do not support the scheduling of this product.

The scheduling of a product on the controlled substances list is done for the purpose of limiting its access. Through various federal control mechanisms (prescribing limits; labeling and reporting requirements) the use of a given product is restricted. That is precisely the intention of the Act. See K.S.A. 65-669, requiring product labels in Kansas to comply with federal law and 65-4121, requiring Kansas doctors and pharmacists to report in accordance with federal law. If a product appears on Schedule IV, the product will require more prescriptions to be written and filled (see 21 CFR Section 1306.22); more reporting to be done by doctors and pharmacists (see 21 CFR Section 1304.11, requiring provider reports to include samples); and special labeling and handling by product distributors (see 21 CFR Section 1302.03, requiring manufacturers to label Schedule IV controlled substances "CIV or C-IV"). How a manufacturer or distributor will handle the problem of packaging products just for the unique labeling requirements of Kansas law is unknown. These are not small problems and they are not without significant impact on patients, providers, manufacturers and distributors.

Samples will no longer be available for, or used by, physicians. K.A.R. 68-20-15a prohibits free distribution of controlled substances to physicians and others. Samples are often used to determine drug performance for particular patients before prescription expenses are incurred and for indigent patients who lack other access to a given product.

Absent thorough and statistically valid research of widespread product abuse, tramadol should not be placed on the schedule of controlled substances. Such action will reduce patient access to this valuable pain reliever and force patients to alternative therapies with greater medical risk and addictive potential.

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Thomas P. Gibson, M.D.
Executive Director
Clinical Affairs

Statement of Dr. Tom Gibson, M.D.
Ortho-McNeil Pharmaceutical
Regarding Kansas House Bill 2225

Tramadol (ULTRAM) is a centrally acting pain reliever with at least two mechanisms of action. One involves weak (much less than morphine) binding to the same receptor to which morphine binds and the other blocks the nerve's reuptake of two compounds important in the perception of pain. ULTRAM was approved by the FDA as a prescription only nonscheduled drug on 3 March 1995 for the treatment of moderate to moderately severe pain. ULTRAM, 50 to 100 mg, can be administered as needed every four to six hours, but the total daily dose should not exceed 400 mg (eight tablets) per day. Therefore, a monthly prescription should not exceed 240 tablets.

Ortho-McNeil Pharmaceutical has promoted ULTRAM for the treatment of chronic, not acute pain. Acute pain can be treated with a number of different analgesics that are available generically, are cheaper, and have a more rapid onset of analgesia. Concerns about the serious gastrointestinal side effects from nonsteriodial antiinflammatory drugs, NSAIDS, with acute use usually are not an issue. Similarly stronger scheduled analgesics are also available generically and can be used acutely because the possibility of addiction is minimal to nonexistent.

Ortho-McNeil believes that ULTRAM is best used to treat patients with moderate to moderately severe pain who are intolerant of the nonsteroidal antiinflammatory drugs. These are patients, most of whom are elderly, who have had a previous history of stomach or duodenal ulcers, have kidney or liver disease or are taking large doses of NSAIDS. It is important to note here that data from several large studies indicate that about 1-4% of patients taking NSAIDS chronically will develop gastrointestinal bleeding and 10% of those may die.

According to a Harris poll reported by the American Medical Association in October of 1994, approximately 17% of the US population suffers from chronic pain. Kansas has approximately 2,600,000 citizens. So this would mean that about 442,000 Kansans have chronic pain. If they were all taking NSAIDS, this would mean that, somewhere between 4420 and 17,680 could have a serious GI complication and 442 to 1768 could die. Tramadol does not affect the protective mechanisms of the gastrointestinal tract an thus offers an alternative therapy.

The FDA agreed that ULTRAM should be a nonscheduled analgesic because data from Germany, where tramadol has been available since 1977, suggested that the abuse potential is low -- approximately 1 to 1.5 patients/100,000 taking it and Ortho-McNeil agreed to establish an independent postmarket surveillance program proactively looking for cases of abuse, defining the at risk population, and designing and implementing interventions to reduce cases of abuse. The program is directed by a committee chaired by Dr. Theodore Cicero of Washington University, St. Louis, and is composed of eight experts on substance abuse, four of whom are physicians. After two years of experience, the committee has found that the reporting rate for abuse, as defined by widely accepted DSM-IV criteria, is exactly what was predicted from the European experience, 1 to 1.5/100,000 patients exposed to ULTRAM. Using the same reasoning as for the gastrointestinal complications of NSAIDS, one might expect that four to five of the 442,000 Kansans with chronic pain, assuming that they have no history of prior drug addiction, could abuse ULTRAM. The independent steering committee found that at least 85% of those patients at risk to abuse ULTRAM are those with a present or past history of drug addiction -- a population that should be readily identifiable by a good medical history. For this reason, our representatives and our promotional material clearly state that ULTRAM should not be used in such patients.

To date, the independent steering committee has identified three cases of ULTRAM abuse in Kansas and two of them were in patients with a past history of substance abuse -- precisely the patient type that should not be given ULTRAM. In the third patient, there is insufficient data to determine their past medical history.

If ULTRAM is scheduled in Kansas market research has demonstrated that physicians will most likely reduce ULTRAM use. As discussed, for certain patient populations, this may be medically inadvisable.

As I mentioned at the beginning, the FDA was willing to work with Ortho-McNeil in establishing an independent postmarket surveillance program. Over the last two years, Ortho-McNeil and the independent committee overseeing the postmarket surveillance program has come to realize that active intervention and education programs can decrease the inappropriate use of ULTRAM in the population at high risk of abusing it -- again those with a past history of abuse or addiction. In March 1996, Ortho-McNeil sent out to over 900,000 health care professionals, a letter defining those at risk of abuse and telling physicians not to use it in such patients. Our representatives and promotional material continually reinforce that message.

In closing, let me reiterate that ULTRAM is an analgesic that meets a need for both patients and physicians. It produces none of the serious and potentially fatal gastrointestinal side effects of NSAIDS that the FDA is now requiring all NSAID manufacturer's to highlight in their package inserts. Tramadol does have a low abuse potential, mainly in those with a previous or present history of addiction, and so Ortho-McNeil warns, in our package insert and promotional material, that ULTRAM not be used in that population. If ULTRAM is scheduled in Kansas, some patients will return to NSAIDS and some will suffer severe consequences that can occur without warning. If a proper medical history is taken, the chance of a patient becoming addicted to ULTRAM is much less that of developing a serious gastrointestinal event. Ortho-McNeil believes that ULTRAM can be used safely in your state and should not be placed on the schedule of controlled substances.

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TO: House Health and Human Services Committee

FROM: Steve Montgomery, Carter-Wallace, Inc.

RE: House Bill No. 2225

DATE: February 17, 1997

Historical Use of Carisoprodol

Carter-Wallace, Inc. (CW), based in the United States, is the manufacturer and distributor of pharmaceutical products throughout the world. Its interest in HB 2225 arises from the proposed scheduling of carisoprodol (trade name: SOMA), a product which CW has marketed as a prescription drug since 1959. Although CW has not had an opportunity to review any clinical data which might be relied upon to support the scheduling of SOMA, the substantial use of this product over 38 years has yielded a substantial amount of data which supports its current non-scheduled status. The position of CW is that scheduling SOMA in Kansas would be inconsistent with the best interests of public health.

SOMA has been marketed since 1959 and SOMA compound (SOMA with aspirin) has been marketed since 1960. A muscle relaxant/analgesic, it is prescribed for the relief of discomfort associated with painful musculoskeletal conditions (e.g., muscle strain and muscle sprain) and is often prescribed as an adjunct to rest, physical therapy, etc. Since 1959, approximately 119 million prescriptions have been written for SOMA and SOMA with aspirin. Approximately 5.2 billion tablets have been dispensed. As you can see, this product has been widely and beneficially used by patients and ample opportunity has existed for gathering clinical data on the use of SOMA.

A Prerequisite to Scheduling Is Objective Scientific Data

Kansas law recognizes that before determining that a drug should be scheduled because of potential for physiologic or psychologic dependence, a thorough scientific review should produce objective data supporting the scheduling. KSA 65-4102(b) imposes upon the Kansas Board of Pharmacy the duty to support proposals for scheduling with scientific study supporting objective scientific data and to publish the supporting objective scientific data. A copy of the statutory requirement, reviewed by the legislature as recently as 1994, is attached to my testimony. To the best of our knowledge, the scientific review required to support the proposed the proposed scheduling of SOMA has not been completed or disclosed. Because the scheduling of drugs must be based upon scientific, rather than anecdotal information, the Board's statutorily required report presents the opportunity for the scientific community to share information and initiate a thorough and objective dialogue of the Board's proposal for scheduling.

The Objective Scientific Data Does Not Support Scheduling SOMA

Without knowledge of whether thorough scientific study has been performed as required by Kansas law, CW is compelled to present to this committee some of the important objective data which has been collected. In a study completed by the National Institute of Mental Health, Addiction Research Center by P.H.S. Hospital in Lexington, Kentucky, SOMA was evaluated for addictiveness. Although the results of the study were quite technical, the base result was that SOMA was not shown to possess addictive qualities.

Further objective data can be found from the FDA spontaneously reported data base for SOMA. A review of this data reveals only 33 reports (out of 88 million prescriptions since the initiation of FDA reporting) regarding dependency. In fact, a number of these reports involved the use of multiple drugs,

including Valium, Darvon, etc. The available data reflects an extremely small number of adverse experiences when compared to the vast clinical use of SOMA.

Scheduling SOMA Will Adversely Impact Patients

When drugs are scheduled, use by patients becomes more tightly restricted. The patient would be taking a drug with the perceived stigma of a narcotic solely because the drug is scheduled and this erroneously implies that the drug could cause dependence and addiction. The prescribing physician also could be affected by this schedule change, because many physicians prefer not to prescribe controlled drugs. Therefore, some clinicians would prescribe unscheduled medication that could be less effective than their drug of choice and this would distort appropriate patient care.

Conclusion

The scheduling of SOMA would be inconsistent with the best interests of public health. The overwhelming available clinical data fails to establish a legitimate basis for scheduling. Scheduling would have an adverse impact on patients in the form of repetitious writings of prescriptions and overall cost. Additionally, CW is still evaluating whether scheduling in Kansas will create special labeling requirements for this state. Carter-Wallace urges the committee to exercise caution and appropriate diligence in the scheduling of SOMA and other pharmaceuticals.

7-3

65-4102. Board of pharmacy to administer act; authority to control; report to speaker of house and president of senate on substances proposed for scheduling, rescheduling or deletion; scheduling of the controlled substance analog.

(b) Annually, the board shall submit to the speaker of the house of representatives and the president of the senate a report on substances proposed by the board for scheduling, rescheduling or deletion by the legislature with respect to any one of the schedules as set forth in this act, and reasons for the proposal shall be submitted by the board therewith. In making a determination regarding the proposal to schedule, reschedule or delete a substance, the board shall consider the following:

(1) the actual or relative potential for abuse;

(2) the scientific evidence of its pharmacological effect, if known;

(3) the state of current scientific knowledge regarding the substance;

(4) the history and current pattern of abuse;

(5) the scope, duration and significance of abuse;

(6) the risk to the public health;

(7) the potential of the substance to produce psychological or psychological dependence liability; and

(8) whether the substance is an immediate precursor of a substance already controlled under this article.

Kansas Association of Osteopathic Medicine

Harold E. Riehm, Executive Director

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February 17, 1997

To: Chairman Mayans and Members, House Public Health Committee

From: Harold E. Riehm, Executive Director, KAOM

Subject: Concerns and Opposition to H.B. 2225

Thank you for this opportunity to present our views on H.B. 2225. We appear with reservations about classification of drugs as provided in this Bill, without further supporting evidence in support of such scheduling.

KAOM has been consistent in its support of scheduling of substances when there is sufficient evidence of a need to protect the public, abuse of a drug, or both.

KAOM, at the same time, has consistently been reluctant to schedule drugs used frequently by member physicians, in the absence of such evidence, or its clear presentation.

In the case of the three drugs/compounds addressed in H.B 2225--CARISOPRODOL (SOMA), BUTORPHANOL (STADOL) AND TRAMADOL (ULTRAM), we think additional information is required before we will support scheduling in Kansas.

We respectfully state our concerns as follows. I will be glad to elaborate on any of these as you wish.

(1) We think the Pharmacy Board has provided insufficient evidence as to the actual or relative potential for abuse, the history and current pattern of abuse in Kansas, the scope, duration and significance of abuse in Kansas, and the risk to the public health in Kansas. These are required by law when efforts are made to schedule or reschedule drugs (KSA 65-4102).

(2) In Kansas, sampling of a controlled substance to a patient is prohibited. Where there is merit in such a provision, we think it heightens the evidence requirements for scheduling new drugs/medications. To varying degrees, we think there remains valid reasons for sampling of at least one of these three drugs and perhaps all three.

(3) When a drug is scheduled, there are distinct criminal penalties for sale, distribution, possession, etc. These are well placed restrictions. However, they must be viewed within the context of physician concern in using such drugs as to potential penalties, prosecution in criminal courts, etc. All of this occurs within a milieu where we know from several national studies that there is under utilization of many pain killing medications, particularly in the treatment of intractable pain. Part of this, we suggest, is due to physician concern of overuse and consequences. Our point here, is that this underscores the care that needs to accompany any decision to schedule drugs. We think evidence for at least one if not all three of these drugs has not been provided in support of passage of this Bill.

I will be pleased to respond to questions.

Stormont-Vail HealthCare
Cotton-O'Neil Clinic

February 17, 1997

Carlos Mayans, Chairman
KANSAS HOUSE HEALTH AND HUMAN SERVICES COMMITTEE
State Capitol Building
300 W. 10th Street
Topeka, KS 66612

Dear Mr. Mayans:

We are writing in reference to the Kansas House Health and Human Services Subcommittee meeting scheduled for Monday, 1/17/97.

It is our understanding that the pharmaceutical tramadol (Ultram) is being considered to become a scheduled prescribed substance in the State of Kansas. We would like to express to you some of our objections to this potential action.

Tramadol is a medication that is used for acute and chronic pain syndromes of various etiologies. If used correctly, it is oftentimes effective in pain reduction in many patients with various types of chronic pain syndromes. In many ways it is safer than other agents that are currently available for treatment of chronic pain. It does not cause propensity for gastritis, peptic ulcer disease, or rare difficulties with renal or hepatic dysfunction that can be seen with nonsteroidal anti-inflammatory agents, and it certainly does not have the amount of addiction potential that is seen with currently scheduled and narcotic pain remedies such as remedies containing codeine, oxycodone or hydrocodone.

There is no recommendation that we are aware of from the FDA that this drug become a scheduled agent. It is our understanding that no other state other than the state of Kansas is even considering this potential change.

The maker of the drug, Ortho-McNeil Pharmaceutical, has supplied information that there is a rare chance of addiction with this medication. This is seen in the vast majority of cases in patients who have already been known to be abusive of other addictive medications or drugs of abuse. If this population is avoided when prescribing this medication, psychological or physical addiction is indeed extremely rarely seen.

In our practices, we have to this point not seen clinically any patients who have had either an apparent physical or psychological addiction to this medication. We have not seen patients requiring or requesting more than the recommended amount of this medication or attempting to have refills of the prescription prior to the time at which they are due. These behaviors are not uncommonly seen with patients who have addiction problems with other prescription remedies. To this point in our practice, this has been a nonexistent problem with tramadol.

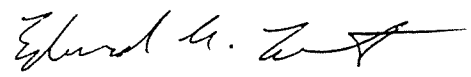
If this medication were to be a controlled substance, it would have several detrimental effects on our practice and on our patients. The psychological stigma of having to use a controlled substance to relieve pain in a medication that is relatively safe for many patients would be unacceptable and they therefore would not avail themselves of what we consider to be a safe pain remedy if used in the usual prescribed parameters. In addition, the pharmaceutical representatives would no longer be able to provide samples for patients to help defray expenses. I think that there would also be a significant chance that if this medication were to become a scheduled substance in the state of Kansas that Ortho-McNeil Pharmaceutical might decide not to provide this medication at all in our state which would be a detriment to many of our patients.

We are not sure why the impetus of this potential action has come forth; we are not aware of any other state or locality which is even giving any consideration to this type of extreme measure.

In many of our patients tramadol has been high successful in relieving their pain and in improving their quality of life with a medication that up to this point has been safe if used in the correct dosages and with the correct precautions. I think the physicians of this state are certainly capable of prescribing it in the correct manner.

In summary, we certainly think that it would be an injustice to our patients to allow this measure to carry forth.

Sincerely,



Edward N. Letourneau, M.D.
Rheumatology
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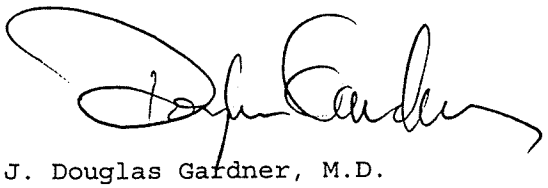
901 S.W. Garfield
Topeka, KS 66606
(913) 354-9591

****AND****



J. Douglas Gardner, M.D.
Rheumatology
Cotton-O'Neil Clinic

ENL/sec

Eric A. Voth, M.D.,FACP
Internal Medicine and Addiction Medicine
901 Garfield
Topeka, Kansas 66606
913-354-0525

Dear Chairman Mayans:

I am writing to strongly oppose the scheduling of Ultram as a scheduled drug. Ultram is extremely useful as a non-psychoactive pain medicine. As such, it has helped to revolutionize the treatment of pain. There exists absolutely no compelling evidence to schedule the drug, and I would urge that the committee reject the measure.

My views are expressed as a specialist in Internal Medicine and Addiction medicine. I treat large numbers of chronic pain patients, and I have also used Ultram usefully for the treatment of pain in addicts without ever documenting a case of abuse. Furthermore, I serve as the chairman of the pharmacy and therapeutics committee for Stormont Vail and St. Francis hospital. To the best of my knowledge, we have never seen behavior that would justify scheduling either.

I urge that the committee reject the scheduling of Ultram.

Sincerely,

Eric A. Voth M.D., FACP

KMS

KANSAS MEDICAL SOCIETY

February 17, 1997

To: House Health and Human Services Committee

From: Meg Henson
Director of Government Affairs

Subj: HB 2288 - Treatment of Obesity

The Kansas Medical Society appreciates the opportunity to appear today on HB 2288, which was introduced at our request, relating to the regulation of obesity drugs by the Board of Healing Arts. The bill would give the board the flexibility to regulate these drugs in accordance with current medical practice. KMS supports this legislation.

Current law in Kansas gives the Board of Healing Arts authority to promulgate rules and regulations governing the "short term treatment of obesity." Until very recently, physicians could legally prescribe obesity drugs for only 90 days per year. As a result of this limit, many physicians simply did not prescribe these drugs for their patients. Many patients traveled across state lines to neighbor states to receive these drugs, where they received little or no monitoring. Other patients "doctor-hopped," seeing one physician for 90 days, then changing physicians and receiving another 90 day cycle, etc. These realities appear inconsistent with the purpose of these laws, which is to protect the public and guard against abuse.

At our request, the Board of Healing Arts promulgated a temporary regulation addressing the use of Redux, a relatively new obesity drug. The regulation allows physicians to prescribe the drug for up to 360 days in a two-year period, which is consistent with the FDA's one year approval of the drug. This regulation was seen as a "temporary fix," addressing the immediate concerns of our members. Because the regulation is temporary, however, it will expire at the end of March. Further, it relates to only one drug. It is our hope that the Legislature will enact this legislation so that the board is given the flexibility to regulate this and other weight loss drugs as new drugs are introduced and practice guidelines change.

HB 2288 is the product of a working group, created by KMS and comprised of physicians, pharmacists, pharmacologists and dieticians who specialize in weight loss treatment. Members of this group expressed a need for giving the board more flexibility than current law allows in treating obesity. When the law was originally enacted in 1984, it reflected current medical practice. Since then, several new drugs have been introduced which have been proven safe for longer periods of time. However, because the law restricts the board's regulation to short term treatment, the board does not feel it has the authority to promulgate rules and regulations to reflect current medical practice.

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Western Kansas office • 311 E 25th St. • Hays KS 67601 • 913.625.8215 • 800.293.2363 • FAX 913.625.8234

KMS believes that some regulation of these drugs is necessary. For this reason, we do not believe that use of these drugs should be unregulated. However, we do believe that the board should be given a flexible regulatory framework to promulgate regulations consistent with current medical practice. The KMS work group has pledged to work with the board to create regulatory language which will protect patients to the fullest extent possible, yet will allow physicians to prescribe these drugs for the benefit of their patients and in accordance with federal law.

Thank you very much for considering our comments. I will be happy to answer any questions.

KANSAS BOARD OF HEALING ARTS

BILL GRAVES
Governor

LAWRENCE T. BUENING, JR.
Executive Director

235 S. Topeka Blvd.
Topeka, KS 66603-3068
(913) 296-7413
FAX # (913) 296-0852

MEMORANDUM

TO: House Committee on Health and Human Services

FROM: Lawrence T. Buening, Jr.
Executive Director

DATE: February 17, 1997

RE: **HOUSE BILL NO. 2288**

Chairman Mayans and committee members, thank you for the opportunity to appear on behalf of the Kansas State Board of Healing Arts in support of House Bill No. 2288. This bill amends K.S.A. 65-2837a of the Healing Arts Act and will allow the Board to determine appropriate limitations on the use of controlled substances for weight loss.

In May, 1995, Readers Digest published an article concerning use of Phentermine and Fenfluramine (Phen/Fen) which is appended as ATTACHMENT 1. Since that time the Board office has received innumerable inquires about the use of these 2 drugs in combination and for longer than 90 days. The Board became acutely aware of the public's interest and demand for Phen/Fen. ATTACHMENT 2 is a copy of an article from the Arkansas Democrat-Gazette dated September 14, 1996 which discusses the problems that might arise when there are no guidelines or when there is a total prohibition.

Because of these inquiries and concerns that Kansas citizens were likewise going to adjacent states which had no restrictions on use of Phen/Fen, the Board in August, 1995, determined it would commence a clinical investigation and allow doctors to apply for and obtain approval to use Phen/Fen. Authority for the project is found at K.S.A. 65-2837a(b)(6). ATTACHMENT 3 is the Patient Worksheet for the clinical investigation which is on-going by the Board. At the present 3,076 patients have been included in the study and the information is being entered into a database which will provide the Board with information on weight loss history, side effects, and geographical demand.

In May, 1996, Redux was approved by the FDA for use in treatment of obesity and was specifically authorized for use beyond 90 days and up to 1 year. Redux is widely publicized as the "hot" new diet pill - see ATTACHMENT 4. Again, in an attempt to meet the needs of the citizens, the Board adopted an amendment to K.A.R. 100-23-1 to enable use of Redux for a period of 360 days in a 2-year period.

K.S.A. 65-2837a was adopted by the 1984 Legislature and was based on a Wisconsin law. The Wisconsin experience reflected that, following adoption of the law, prescriptions for amphetamines and sympathomimetic amines decreased by 90%. The Kansas law makes use of schedule II drugs for treatment of obesity unlawful. However, recent studies and continuing medical advances may make weight control drugs safe and effective both in combination, like Phen/Fen. or for extended periods like Redux.

Regulation of a physician's prescribing practice is a critical public policy decision. The Board is of the opinion that some controls are appropriate, but that a mechanism needs to exist to allow guidelines and standards to change along with the medical advances. ATTACHMENT 5 is a copy of the Practice Guidelines of the American Society of Bariatric Physicians.

Thank you for the opportunity to appear before you in support of House Bill No. 2288. I would be happy to respond to any questions.

May 1995 $2.25

Reader's Digest

World's Most Widely Read Magazine

WELFARE GONE HAYWIRE
PAGE 92

RETURN OF A GOLDEN KNIGHT
PAGE 124

JOURNEY TO THE WINNER'S CIRCLE
PAGE 86

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ATTACHMENT 1

12-3

ATTACHMENT 2

AR-0190 DAILY NEWSPAPER
ARKANSAS DEMOCRAT-GAZETTE
Little Rock, AR

Circ-(M) 179,609 (S) 292,057

SEPTEMBER 14, 1996

Bacon's

2947

Panel votes to suspend diet doctor

BY KAREN McALLISTER
Democrat-Gazette Health Writer

The Arkansas State Medical Board voted Friday to suspend the license of an Osceola doctor who prescribed diet pills to 613 patients in one day last month.

Medical Board attorney William H. Trice III said Dr. George Pollock will continue to hold his license until the board prepares an order and serves the doctor with papers at his clinic.

"Even if it is legitimate treatment, it would be hard to provide adequate care at that rate," Trice said.

Pollock will have a hearing before the board at its December meeting.

Since July, Pollock has been prescribing fen-phen — a combination of appetite suppressants — to patients at least 9 pounds overweight. Pollock said he charges patients $35 and does not give physical exams before writing prescriptions for Fenflauimine and Phentermine. He sees patients individually only by special request.

Sixty to 70 percent of Pollock's patients travel to his clinic from Tennessee, where doctors are

See LICENSE, Page 14A

Arkansas Democrat-Gazette

2947 cont

License

• Continued from Page 1A

prohibited from prescribing the drugs.

In an interview at his office Tuesday, Pollock said he stays too busy for one-on-one consultations and in March started using a video to introduce patients to his diet plan.

Health Department investigators visited Pollock's office recently on behalf of the medical board. On Tuesday, Pollock said he was assured there were no problems with his practice.

"I know more about this than anyone on the medical board," Pollock said.

When Pollock learned Friday about the board's emergency suspension, he said, "I have a bunch of patients depending on me. I think this is terrible."

The fen-phen combination is selling out throughout the country, and its popularity has spawned an industry of diet clinics. Since Pollock started prescribing the combination, two specialty clinics have opened in West Memphis.

Both drugs are legal in Arkansas, but state and federal law prohibits doctors from prescribing drugs without a legitimate medical reason and appropriate medical exams. A federal Drug Enforcement Agency investigator said the agency is investigating fen-phen clinics in Northeast Arkansas but would not say whether Pollock was the subject of an inquiry.

Pollock initially greets his patients through a 12-minute video played in a room lined with folding chairs. On a first visit, a nurse weighs patients and checks their blood pressure. Patients are then escorted in groups of up to 30 to a waiting room to watch Pollock's video. Pollock then meets the group to talk about his program and the drugs' side effects.

The session concludes with Pollock calling out names and distributing fen-phen prescriptions. He advises patients to return each month for refills. On return visits, a nurse weighs the patient and checks vital signs.

On Tuesday, office manager Dorothy Crockett talked to groups about their weight loss, answered questions and distributed prescriptions.

Pollock said he is dealing only with patients' obesity and suggests they get physicals from their primary-care doctor.

Nancy Grace, who has traveled from Jackson, Tenn., twice to Pollock's office, said she didn't mind not meeting with the doctor privately.

"When I first came here I just wanted to get out and try it," said Grace, who lost 12 pounds in her first month on the program and hopes to lose 30 more. Grace took a vacation day from her factory job to avoid the Saturday crowds at the Osceola clinic.

Fenflauimine kills appetite but leaves patients drowsy, while Phentermine speeds up metabolism and reportedly acts as an "upper."

Both drugs have been on the market and sold separately for more than 30 years. They became popular in the early 1990s after Dr. Michael Weintraub received a National Institute of Health grant to study them as part of a total medical treatment for obesity.

Pollock said his fen-phen business evolved as patients demanded the prescriptions. Word spread quickly after he first prescribed the combination in July 1995. By January 1996, Pollock was seeing up to 66 patients a day and by August, an average of 200 a day. On Aug. 3 — a Saturday — Pollock wrote prescriptions for 613 patients.

Pollock repeatedly said, "I'm not running them through like cattle."

On Sept. 9, the Osceola Wal-Mart filled 500 prescriptions for Fenflauimine and Phentermine, said pharmacist Leigh Ann Ross. The two prescriptions — sold under the trade names Pondimin and Ionamin — cost about $80.

Pollock gives his patients a list of 22 potential side effects, including severe dizziness, chest pains, hyperactivity, rapid heartbeat, and blurred vision. Pollock and patients said the drugs curb their appetites so much that they have to remind themselves to eat.

12-4

PHEN - FEN RESEARCH PROJECT

PATIENT WORKSHEET

PATIENT NAME _____

PATIENT ID ___ ___ ___ - ___ ___ ___

PHYSICIAN NAME _____

PHYSICIAN COUNTY _____

INTERVAL	WEIGHT	SIDE EFFECT CODE	DATE
INITIAL			
THREE MONTH			
SIX MONTH			
NINE MONTH			
TWELVE MONTH			
18 MONTH			
TERMINATION			

TERMINATION REASON (circle one)	achieved weight loss goal	side effects	unknown	other (explain below)

SIDE EFFECTS (Circle all that apply):

A none	B dry mouth, unpleasant taste	C headache	D heart palpitations, tachycardia	E restlessness, insomnia	F impotence, change in libido	G Other

SIDE EFFECTS:
(NARRATIVE)

DISQUALIFICATIONS:
(NARRATIVE)

AMERICAN SOCIETY OF BARIATRIC PHYSICIANS

BARIATRIC PRACTICE GUIDELINES

AMERICAN SOCIETY OF BARIATRIC PHYSICIANS
5600 S. Quebec Street
Suite 109A
Englewood, CO 80111
(303) 770-2526

Adopted 1974
Revised 1979, 1982, 1988, 1991, 1996

BARIATRIC PRACTICE GUIDELINES
American Society of Bariatric Physicians

These guidelines provide suggestions for the work-up and follow-up of the bariatric patient. They are not intended to replace, and indeed cannot replace, the bariatrician's judgement regarding a particular patient's treatment. Neither are they intended to represent legal requirements for providing "good medical practice." The bariatrician is the one most capable of determining what is or is not appropriate for an individual patient.

A. Initial Patient Work Up

The course of treatment should be based on the patient's history, physical examination, laboratory work and ECG (when indicated).

1. **History**
   A history of each patient should be taken and recorded. It should include an evaluation of dietary status, a weight history and a history of mental status. Whenever this is a self fill-in, or computerized history, or one taken by assistants, the bariatrician should personally evaluate significant positive responses and make appropriate notations.

2. **Physical Examination**
   The physical examination should include the following:
   a. Height, weight, blood pressure and pulse.
   b. Additional examinations should be done which are appropriate for the patient's age and state of health. Usually this would include examinations of the head, neck, thyroid, heart, lungs, abdomen and extremities. The patient's records should indicate the status of observations made.

3. **Diagnostic Studies**
   a. Laboratory Work:
      An "executive-type" profile including testing for thyroid function (TSH suggested) should be completed in addition to other laboratory work if indicated.
   b. Electrocardiogram:
      The bariatrician should consider the potential benefits of obtaining an electrocardiogram if there is past or present evidence of cardiac disease and if the patient has coronary risk factors such as hypertension, hyperglycemia, dyslipidemia or a strong family history of cardiac disease.
   c. Optional Tests:
      Body composition using skinfolds, infrared or impedance testing may be performed as additional testing. Other tests may be included at the discretion of the bariatrician.

4. **Patient Counseling**
   Appropriate counseling should be given to patients on proper eating habits, exercise, behavior modification, medications and other aspects of therapy, prior to and during the weight loss program.

When prior medical records can be obtained indicating any of the above procedures have recently been completed, the bariatrician may avoid unnecessary duplication by performing only those exams needed to complete the bariatric work-up.

5. **Return Visits**
   The bariatrician should provide adequate periodic follow-up and counseling for the patient.

B. Medications and Other Therapeutic Modalities

1. The bariatrician should weigh the potential benefits and risks of any medication or modality used. Significant sources of such information include journal articles, experience of colleagues, labeling, textbooks, The ASBP Anorectic Usage Guidelines and personal education, training and experience. Each of these sources may provide valuable information, and no single source should be used to the exclusion of others.

2. When appropriate, the bariatrician should provide information on the benefits and risks of the proposed treatment modalities to be used and should inquire as to the patient's understanding of the benefits and risks.

3. When medications are dispensed, they should be packaged and labeled in accordance with applicable laws and appropriate records should be kept.

C. Maintenance

A program, as developed by the individual bariatrician, should be provided for helping the patient in maintaining the weight loss that has been achieved.