

GARY D. COLBY, Ph.D., J.D.
DIRECT DIAL: 215.979.1849
E-MAIL: GDColby@DuaneMorris.com

0350 5 OCT 19 A7:31

www.duanemorris.com

NEW YORK
LONDON
LOS ANGELES
CHICAGO
HOUSTON
PHILADELPHIA
SAN DIEGO
SAN FRANCISCO
BOSTON
WASHINGTON, DC
ATLANTA
MIAMI
PITTSBURGH
NEWARK
ALLENTOWN
WILMINGTON
HARRISBURG
PRINCETON
WESTCHESTER

19 October 2005

VIA FEDEX

Division of Docket's Management
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: **CITIZEN PETITION**

Dear Sir/Madam:

The undersigned submits this petition in quadruplicate on behalf of a client under 21 CFR 10.30 or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs, including under 21 CFR 5.10, to request the Commissioner of Food and Drugs to: i) re-evaluate the prescribing information/package insert for new tramadol formulations in light of currently available safety information and ii) designate extended release formulations of tramadol (Tramadol ER) as Schedule III drugs under the Controlled Substances Act of 1970, as amended.

A. Action Requested

The Petitioner requests that the Commissioner of Food and Drugs:

1. Re-evaluate the prescribing information/package insert for new tramadol formulations in light of currently available safety information.

and

2. Designate or recommend designation of extended release formulations of tramadol (Tramadol ER) as Schedule III drugs under the Controlled Substances Act of 1970, as amended.

B. Statement of Grounds

(i) Overview

Several companies are developing extended release once-a-day formulations of tramadol. The FDA has recently approved one formulation of Tramadol ER; other

2005P.0421

CP1

formulations are expected to be approved over the next few years. These formulations will undoubtedly be the subject extensive sales, marketing and physician sampling efforts, particularly in view of the void created by the recent withdrawal of Vioxx[®] and Bextra[®], and the genericization of Ultram[®], Ultracet[®], OxyContin[®] and Duragesic[®].

Tramadol ER carries all the documented adverse effects and abuse potential of immediate release (I.R.) tramadol, combined with new safety considerations by way of its extended release profile. The latter has come into particular focus due to the abuse of OxyContin. Experience with OxyContin has shown that intentional crushing or extraction of the active ingredient from the formulation by addicts and recreational drug users destroys the controlled-release mechanism and results in a rapid surge of drug into the bloodstream. Serious side-effects and death have been reported from such misuse. In addition to the potential for such effects with Tramadol ER, high concentrations of tramadol, especially in combination with many popular antidepressants (which are ubiquitous in the setting of chronic pain) can produce serotonin syndrome. If not properly diagnosed and treated, serotonin syndrome can lead to life-threatening complications and death.

Tramadol is a synthetic, centrally acting analgesic which exerts its analgesic effects by inhibiting reuptake of norepinephrine and serotonin and by activation of μ -opioid receptors. Tramadol binds to the μ -opioid receptor, although its principal active (M1) metabolite, mono-O-demethyl-tramadol is up to 6 times more potent in producing analgesia and 200 times more potent in μ -opioid binding (Ultram Package Insert).

In the United States, tramadol is presently available as an oral I.R. single-entity tablet (Ultram, others) and as a fixed-dose combination with acetaminophen (Ultracet[®], others). The approved indication for single-entity oral tramadol is "for the management of moderate to moderately severe pain." The approved indication for Ultracet is for the "short-term (five days or less) management of acute pain". It should be noted that due to the genericization of Ultram, there has been not been any significant physician sampling or promotion of I.R. tramadol for several years. This will change with the introduction branded Tramadol ER formulations from various companies. Recently, FDA has approved a new Tramadol ER formulation from Biovail Laboratories in strengths of 100, 200 and 300 mg tablets for the indication of "moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time." This product is not yet marketed.

Receptor binding and pharmacologic evaluations in a variety of non-clinical models of opioid abuse and dependence provide compelling evidence that tramadol and its M1 metabolite bind to the opioid receptor, substitute for morphine and attenuate or suppresses morphine abstinence.

Data from FDA, the Drug Enforcement Administration (DEA), the Drug Abuse Warning Network (DAWN), the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS), National Survey on Drug Use and Health (NSDUH) and other credible sources indicate that tramadol is widely abused. Surprisingly, the innovator funded surveillance studies for I.R. tramadol are "outliers" in suggesting minimal risk of abuse and drug addiction (Cicero et al, 1999; Knisely et al, 2000;).

(ii) Nonclinical Pharmacology Indicates Classic Opioid and Serotonin Effects

Tramadol avidly binds to the μ -receptor. Its principal active metabolite, mono-O-demethyl-tramadol (M1) is up to 6 times more potent than the parent drug in producing analgesia and 200 times more potent in μ -opioid binding (Desmeules et al., 1996; Hennies et al., 1988; Raffa et al., 1992).

The analgesic effect of tramadol in the tail flick test in rats and mice are partially antagonized by naloxone (Carlsson & Jurna., 1987; Kayser et al., 1991; Raffa et al., 1992). Pretreatment with tramadol in mice and rats results in withdrawal symptoms induced by opioid antagonist challenge, including the Straub tail phenomena, withdrawal jumping and loss of bodyweight (Friderichs et al. 1978; Murano et al. 1978; Nickel & Aledter 1987). Similarly, administration of naloxone to monkeys who receiving 8 weeks of treatment with progressively increasing doses of tramadol up to 100 mg/kg daily results in classic signs of opioid withdrawal (Yanagita 1978). In continuous self-administration experiments with naive and conditioned monkeys, tramadol has a reinforcing effect (Yanagita 1978).

Replacement of tramadol with the opioid antagonists levallorphan and naloxone precipitate weight loss in rats and characteristic signs of opioid withdrawal in mice and rats (Friederichs et al., 1978, Murano et al., 1978; Wakasa et al., 1994).

Tramadol fully substitutes for morphine at high doses in a rat model of dependence and this effect is antagonized by the opioid antagonist, naltrexone (Ren and Zheng, 2000). Other studies have suggested that tramadol only partially substitutes for morphine in animal models. An important consideration is the selection of tramadol dose and the role its principal active metabolite (M1), which accumulates with repeated dosing and would undoubtedly be a C-II scheduled drug if it were commercialized in the USA.

(iii) Epidemiologic Data Demonstrate Abuse and Addiction Potential

According to the Drug Enforcement Administration, "Tramadol is abused for its opiate effects. The current pattern of tramadol abuse in the US involves street drug

addicts, chronic pain patients, and health professionals. As an uncontrolled substance, there are no Controlled Substance Act regulations regarding manufacturing, distribution, or prescription of this medication.” (http://www.deadiversion.usdoj.gov/drugs_concern/tramadol.htm). DEA cites the Drug Abuse Warning Network (DAWN) data for drug related hospital emergency room episodes. In 2002, there were 1,714 episodes for tramadol and a total of 7,890 episodes from 1998 through 2002. DAWN medical examiners reported that tramadol was involved in 95 drug-related deaths in 2002 and a total of 382 deaths from 1998 through 2002.

According to the 2002 National Survey on Drug Use and Health (NSDUH), approximately one million individuals have taken tramadol (Ultram) for non-medical use. This is approximately the same incidence of non-medical use reported for Dilaudid® and approximately 50% of the incidence reported for OxyContin. Among non-medical OxyContin users, 18.3% also reported consuming Ultram for non-medical reasons.

In the two most recent annual reports of the American Association of Poison Control Centers Surveillance System (TESS), tramadol ranked only second to oxycodone in the number of opioid exposure cases (Watson et al, 2002).

A study published in the September 2004 issue of the Journal of Forensic Sciences of 66 deaths in which short-acting tramadol was detected in the decedent's blood notes that "...tramadol may be a significant contributor to lethal intoxication when taken in excess with other drugs ...". The study discusses the role of opioid and serotonin effects in such deaths (Clarkson et al, 2004)

According to a recent report in JAMA regarding drugs abused by physicians, tramadol was the third most frequently mentioned abused opioid. It was more frequently mentioned than was fentanyl, oxycodone or hydromorphone (Skipper et al, 2004; Skipper et al, 2005; Adams et al., 2005).

The FDA's Medwatch system has received approximately a 1000 domestic adverse-event reports for tramadol coded as "drug dependence", "drug withdrawal" or "drug abuse" (Brinker et al, 2002).

There are also numerous reports in the literature of drug abuse, addiction., physical dependence, seizures and withdrawal on abrupt cessation with tramadol (Barsotti et al, 2003; Brinker A et al, 2002; Ehrenreich and Poser, 1993; Freye and Levy, 2000; Leo et al, 2000; Liu et al, 1999; Marquardt et al, 2005; Reeves and Liberto, 2001; Ripamonti et al, 2004; Rodriguez Villamanan, et al 2000; Prescrire Int. 2003; Prescrire Int. 2005; Scherbaum et al, 2005; Senay et al, 2003; Thomas and Suresh, 2000; Soyka et al, 2004; Yates et al, 2001; Zacny, 2005)

Tramadol has also been found to be effective in substituting for or treating moderate heroin withdrawal, with efficacy comparable to buprenorphine and superior to clonidine (Tamaskar et al, 2003; Sobey et al, 2003).

(iv) Extended-Release Formulations May Present New Safety Consideration

Tramadol's pain relieving effects are due to serotonin and norepinephrine reuptake inhibition, and through an opioid effect. Tramadol is an unscheduled narcotic, therefore it is readily available like any ordinary prescription drug.

Commercially available I.R. tramadol (Ultram) releases 50 mg of tramadol per tablet into the systemic circulation over several hours. New, extended release formulations are designed to gradually release their much larger tramadol content over a 24-hour period. Consequently, prior postmarketing surveillance from I.R may not fully predict the abuse potential of the new Tramadol ER formulations. Experience with OxyContin would suggest that if formulations of Tramadol ER are tampered, the entire 24-hour drug supply may be released into the bloodstream, with resulting potential for toxic effects.

Most recreational drug users and addicts have a unit of use which is one tablet or capsule. The 24-hour supply of tramadol contained in one tablet, instead of 4 to 6 tablets means that there is a risk that such formulations may be highly sought by drug addicts and recreational drug users alike for non-medical use. Intentional tampering from Tramadol ER formulations has the potential to rapidly deliver a massive dose and produce neurological toxicity, including agitation, seizures, coma and respiratory failure from both from opioid and serotonergic mechanisms.

During its non-medical use by drug addicts and recreational users, Tramadol ER is likely to be crushed to provide maximum opioid effects. Since tramadol produces dose dependent seizures and dose dependent serotonin syndrome, there is the potential for a compounded risk. The occurrence of serotonin syndrome has been well documented with tramadol given alone, with serious and potentially fatal consequences (Clarkson et al, 2004; Garrett, 2004; Kitson and Carr, 2005). The sudden exposure of patients to large concentrations of tramadol from crushed solid dosage forms of Tramadol ER, especially in the face of ubiquitous use of SSRI's and SNRI's in chronic pain may have important medical consequences. (Clarkson et al, 2004; Gonzalez-Pinto et al, 2001; Houlihan, 2004; Egberts et al, 1997; Kesavan and Sobala, 1999; Lange-Asschenfeldt, 2002; Mahlberg et al, 2004; Mittino et al, 2004). These are additional reasons to require C-III scheduling for Tramadol ER.

(v) Schedule for Tramadol

It is widely known in the pharmaceutical industry and amongst clinicians that Schedule II status results in maximal prescribing restraint and that only Schedule II and Schedule III have "teeth". The Petitioner recommends that FDA seriously consider a minimum Schedule III status for Tramadol. Any less stringent a controlled substance schedule is widely considered to be inadequate. The recent decision of the FDA and DEA to reschedule buprenorphine from C-V to C-III is consistent with the Petitioners request. In addition, abuse liability issues are often regional or national in nature; evidence would suggest that the magnitude of diversion and abuse of OxyContin was particularly high in the United States. Consequently, scheduling decisions need to reflect the potential risk in the context of the American environment.

(vi) Comprehensive Safety Assessment and Label Review Needed

Tramadol I.R. formulations have a role in the treatment of acute and chronic pain, and Tramadol ER formulations have utility in the treatment of chronic pain; they provide clinicians with an alternative treatment option for patients unresponsive to other drugs. Since the commercialization of Ultram approximately 10 years ago, the therapeutic landscape has changed significantly. There is widespread use of non-TCA antidepressants to treat a wide variety of affective disorders, including co-morbid depression in patients with chronic pain and as adjuvant analgesics ("off-label"). Although the concurrent use of SSRI's, SNRI's and TCA's and tramadol is contraindicated, there continues to be widespread concomitant use. New evidence suggests that there is a risk of serotonin excess from such concurrent use, resulting in serotonin syndrome. Further, with the use of Tramadol ER, intentional crushing of the formulation may result in a dose dependent increase in the risk of serotonin syndrome, overdose and seizures. These potential risks, which may be unique to Tramadol ER, need careful evaluation in the context of all available safety information. The risk may not have been fully evaluated in clinical trials of Tramadol ER due to the exclusion of study subjects taking concurrent SSRI's, SNRI's and TCA's.

(vii) Legitimate Role for Opioids: Achieving an Appropriate Balance

The Petitioner believes that recent experience with opioid drug diversion and drug abuse, and associated public health implications warrant prudent regulatory practices, notwithstanding any commercial implications to pharmaceutical companies. A C-III status for tramadol means that clinicians will think very carefully about the risk benefit profile of the drug in the specific patient, every time they write a prescription for tramadol ER. A C-III schedule provides an appropriate balance between the rights of patient's with pain to access Tramadol ER, while safeguarding public safety.

The Petitioner believes that this may be the final regulatory opportunity to meaningfully evaluate the safety of Tramadol ER, both in terms of the adequacy of the prescribing information and the scheduling of Tramadol ER as a C-III drug, particularly in light of lessons learned from our experience with oxycodone ER (OxyContin) and other analgesics.

C. Environmental Impact

The action requested by the Petitioner is exempt from the requirements for an Environmental impact Statement or an Environmental Assessment under 21 CFR 25.31.

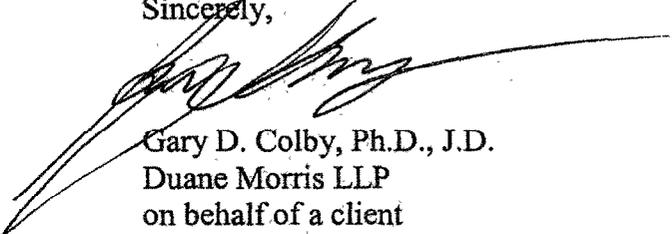
D. Economic Impact

The Petitioner does not believe that an economic impact statement is applicable, but will agree to provide such an analysis if requested by the Commissioner in accordance with 21 CFR 10.30(b).

E. Certification

The undersigned certifies that to the best knowledge of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,



Gary D. Colby, Ph.D., J.D.
Duane Morris LLP
on behalf of a client

Attachment: References

Copy to (letter only):

Dr. Bob Rappaport, Division of Anesthesia, Analgesia & Rheumatology Products, FDA
Dr. Deborah Leiderman, Director, Controlled Substance Staff, FDA

REFERENCES

- Adams EH, Dart RC, Knisley JS, et al. Tramadol abuse by physicians and dependence among physicians. *JAMA* 2005;293:1977.
- Barsotti CE, Mycyk MB, Reyes J. Withdrawal syndrome from tramadol hydrochloride. *Am J Emerg Med* 2003;21:87-8.
- Brinker A, Bonnel RA, Beitz J. Abuse, dependence, or withdrawal associated with tramadol. *Am J Psychiatry* 2002;159:881-82.
- Carlsson KH, Jurna I. Effects of tramadol on motor and sensory responses of the spinal nociceptive system in the rat. *Eur J Pharmacol* 1987;139:1-10.
- Cicero TJ, Adams EH, Geller A et al. A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. *Drug Alcohol Depend.* 1999;57:7-22.
- Clarkson JE, Lacy JM, Fligner CL, et al. Tramadol (Ultram) concentrations in death investigation and impaired driving cases and their significance. *J Forensic Sci* 2004;49:1101-5.
- Desmeules JA, Piguet V, Collart L, Dayer P. Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol.* 1996;41:7-12.
- Egberts ACG, ter Borgh J, Brodie-Meijer CCE. Serotonin syndrome attributed to tramadol addition to paroxetine therapy. *In J Clinical Psychopharmacol* 1997;12:181-82.
- Ehrenreich H, Poser W. Dependence on tramadol. *Clin Investig* 1993;72:76.
- Freye E, Levy J. Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): a case study. *Eur J Pain* 2000;4:307-11.
- Friederichs VE, Felgenhauer F, Jongschaap P et al. Pharmacologic studies on analgesia, dependence on and tolerance of tramadol, a potent analgesic drug. *Arzneim Forsch* 1978; 28:122-134.
- Garrett PM. Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. *Anaesth Intensive Care* 2004;32:575-77.
- Gonzalez-Pinto A, Imaz H, De Heredia JL, Gutierrez M, Mico JA. Mania and tramadol-fluoxetine combination. *Am J Psychiatry.* 2001;158:964-5.
- Hennies HH, Friederichs E, Wilsmann K et al. Effect of the opioid analgesic tramadol on inactivation of norepinephrine and serotonin. *Biochemical Pharmacol* 1982;31:1654-1655.
- Houlihan DJ. Serotonin syndrome resulting from coadministration of tramadol, venlafaxine, and mirtazapine. *Ann Pharmacother* 2004;38:411-13.
- Kayser V, Besson J-M, Guilbaud G. Effects of the analgesic agent tramadol in normal and arthritic rats: Comparison with the effects of different opioids, including tolerance and cross-tolerance to morphine. *Eur J Pharmacol* 1991;195:37-45.
- Kesevan S, Sobala GM. Serotonin syndrome with fluoxetine plus tramadol. *J R Soc Med* 1999;92:474-75.

Kitson R, Carr B. Tramadol and severe serotonin syndrome. *Anaesthesia* 2005;60:928-29.

Knisely JS, Campbell ED, Dawson KS, Schnoll SH. Tramadol post-marketing surveillance in health care professionals. *Drug Alcohol Depend.* 2002;68:15-22.

Lange-Asschenfeldt C, Weigmann H, Hiemke C, Mann K. Serotonin syndrome as a result of fluoxetine in a patient with tramadol abuse: plasma level correlated symptomatology. *J Clin Psychopharmacol* 2002;22:440-41.

Leo RJ, Marendran R, DeGuiseppe B. Methadone detoxification of tramadol dependence. *J Subst Abuse Treat* 2000;19:297-9.

Liu ZM, Zhou WH, Lian Z, Mu Y, Ren ZH, Cao JQ, Cai ZJ. Drug dependence and abuse potential of tramadol. *Zhongguo Yao Li Xue Bao* 1999;20:52-4.

Mahlberg R, Kunz D, Sasse J, Kirchheiner J. Serotonin syndrome with tramadol and citalopram. *Am J Psychiatry* 1004;161:1129.

Marquardt KA, Alsop JA, Albertson TE. Tramadol exposures reported to statewide poison control system. *Ann Pharmacother.* 2005;39:1039-44.

Mittino D, Mula M, Monaco F. Serotonin syndrome associated with tramadol-sertaline coadministration.. *Clin Neuropharmacol* 2004;27:150-51.

Murano T, Yamamoto H, Endo N et al. Studies on dependence on tramadol in rats. *Arzneimittel-Forschung-Drug Research* 1978;28: 152-158.

Nickel B, Aledter A. Comparative physical dependence studies in rats with flupirtine and opiate receptor stimulating analgesics. *Postgraduate Medical Journal* 1987;63:41-43

Prescrire Int. 2003;12(65):99-100. withdrawal syndrome and dependence: tramadol too.

Prescrire Int 2004 Apr;13(70):57. Venlafaxine + tramadol: serotonin syndrome.

Prescrire Int. 2005;14(77):103. Tramadol Addiction.

Raffa RB, Friederichs D, Reimann W et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* 1992;260:275-285.

Reeves RR, Liberto V. Abuse of combinations of carisoprodol and tramadol. *South Med J.* 2001;94:512-4.

Ren YH, Zheng JW. Influence of tramadol on morphine discriminative behaviour in rats. *Acta Pharmacol Sin* 2000;21:924-26.

Ripamonti C, Fagnoni E, De Conno F. Withdrawal syndrome after delayed tramadol intake. *Am J Psychiatry* 2004;161:2326-27.

Rodriguez Villamanan JC, Albaladejo Blanco C, Sanchez Sanchez A, Carvajal A, Martin Arias L, Carcia del Pozo, J. Withdrawal syndrome after long-term treatment with tramadol. *Br J Gen Pract* 2000;50:406.

Scherbaum N, Kluwig J, Meiering C, Gastpar M. Use of illegally acquired medical opioids by opiate-dependent patients in detoxification treatment. *Eur Addict Res.* 2005;11:193-6.

Senay EC, Adams EH, Geller A et al. Physical dependence on Ultram (tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug Alcohol Depend.* 2003;69:233-41.

Skipper GE, Fletcher C, Rocha-Judd R. Tramadol abuse and dependence among physicians. *JAMA* 2004;292:1818-19.

Skipper GE. Tramadol abuse by physicians and dependence among physicians. (Reply). *JAMA* 2005;293:1977-78.

Sobey PW, Parran TV Jr, Grey SF et al. The use of tramadol for acute heroin withdrawal: a comparison to clonidine. *J Addict Dis.* 2003;22:13-25.

Soyka M, Backmund M, Hasemann S. Tramadol use and dependence in chronic noncancer pain patients. *Pharmacopsychiatry* 2004;37:191-92.

Tamaskar R, Paron TV, Heggi A, Brateanu A, Rabb M, Yu J. Tramadol versus buprenorphine for the treatment of opiate withdrawal: a retrospective cohort control study. *J addict Dis* 2003;22:5-12.

Thomas AN, Suresh M. Opiate withdrawal after tramadol and patient-controlled analgesia. *Anaesthesia* 2000;55:826-7.

Ultram package insert. Physicians' Desk Reference, 2005, Thomson PDR, Montvale, NJ

Wakasa Y, Kawaguchi T, Yanagita T. Withdrawal characteristics following frequent intravenous administration of several opioids in rats. *Japan J Alcohol & Drug Dependence* 1994;29:40-51.

Watson WA, Litovitz TL, Rodgers GC, et al. 2002 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2003;21;353-421.

Yanagita T. Drug dependence potential of 1-(m-Methoxyphenyl)-2-(dimethyl aminomethyl)-cyclohexan-1-ol Hydrochloride (Tramadol) tested in monkeys. *Arzneimittel-Forschung-Drug Research* 1978;28:158-63.

Yates WR, Nguyen MH, Warnock JK. Tramadol dependence with no history of substance abuse. *Am J Psychiatry* 2001;158:964-5.

Yates T. Abuse, dependence, or withdrawal associated with tramadol. (Reply). *Am J Psychiatry* 2002;159;881-82.

Zacny JP. Profiling the subjective, psychomotor, and physiological effects of tramadol in recreational drug users. *Drug Alcohol Depend.* 2005;80:273-8.

ATTACHMENTS