PriCara
Unit of Ortho-McNeil, Inc.

1000 Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602
908-218-6000 Telephone
www.pricara.com

January 12, 2006

Food and Drug Administration
Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. 2005N-0479: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Butorphanol; Delta-9-tetrahydrocannabinol (Dronabinol); Gamma-Hydroxybutyric Acid; Ketamine; Khat; Tramadol; Zopiclone; Buprenorphine; Oripavine. 70 Fed. Reg. 73,775 (Dec. 13, 2005).

Dear Sirs:

This responds to the Federal Register notice dated December 13, 2005, in which the FDA requested information to answer a questionnaire issued by WHO. WHO announced that it will hold a meeting of its Expert Committee on Drug Dependence (ECDD) on March 28, 2006 and has said that one of the substances that will be given critical review at that meeting is tramadol, a medicine for the management of moderate to moderately severe pain in adults. This response will present information concerning tramadol on behalf of Ortho-McNeil, Inc. which markets this medicine.

Sincerely,

Gary J Vorsanger, PhD., M.D.
Senior Director, Clinical Development
PriCara, a Unit of Ortho-McNeil, Inc.

2005N-0479

C 5

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket No. 2005N-0479, International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs ... tramadol .... 70 Fed. Reg. 73,775 (Dec. 13, 2005).

I. BACKGROUND

It is unclear why tramadol appears on the agenda for the March 2006 ECDD meeting. The substance was given a critical review by the ECDD that met in 2002, and the report of that meeting contains the recommendation of the committee. The 2002 ECDD recommended no scheduling of tramadol. The work of the 2002 ECDD completed the cycle contemplated by WHO's rules, which are contained in the document entitled "*Guidelines for the WHO review of dependence-producing psychoactive substances for international control (Guidelines)*." That cycle requires, for most critical reviews, a pre-review to be followed by the critical review. Paragraph 15 is the pertinent provision of the *Guidelines*:

> *Critical Review*
>
> *15. Critical review is conducted by the Expert Committee in any of the following cases: (1) there has been notification from a Party to the 1961 or the 1971 Convention concerning the scheduling of a substance; (2) there has been an explicit request from CND to review a substance; (3) pre-review of a substance has resulted in a recommendation for critical review as indicated in paragraph 13 above; (4) information is brought to WHO's attention that a substance is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any Member State. If therapeutic use of the substance is confirmed subsequently by any Member State in respect of case (4), the substance shall be subjected to a pre-review.*

These criteria have been explicitly recognized at page 4 of the official report of the most recent ECDD, which met in 2002. Expert Committee on Drug Dependence, World Health Organization, Thirty-third Report (2003). None of the four conditions for a critical review has been met.

The recommendation of the 2002 ECDD concerning tramadol was, specifically: "The information available is not sufficient for the Committee to recommend international control of tramadol, but is

adequate to recommend that WHO keep the drug under surveillance." In its letter to Dr. William Steiger of HHS, WHO has justified placing tramadol on the agenda of the March 2006 as follows, referring to the report of the 2002 ECDD: "In the case of tramadol, the Committee recommended that the subject would be placed on the agenda again ...." Letter from Dr. Vladimir K. Lepakhin, Assistant Director-General, Health Technology and Pharmaceuticals, to Dr. William R. Steiger, Special Assistant to the Secretary for International Affairs, Office of Global Health Affairs (Nov. 16, 2005). This is a strange interpretation of what the ECDD said. If words are to be given their ordinary meaning, recommending that the drug be kept "under surveillance" does not equate to saying that it should "be placed on the agenda again."

If the plain meaning of the words is unpersuasive, the record of WHO and the ECDD directly contradicts WHO's own and very recent interpretation of the meaning of the admonition to keep a drug "under surveillance." The drug diazepam was subjected to a pre-review in 1998 by the 31st ECDD, which recommended a critical review. The critical review occurred at the next meeting, in 2000, and, just as it did with tramadol in 2002, the ECDD recommended no change in the scheduling of diazepam; the report did, however, state: "... [T]he Committee recommended that WHO continue to keep diazepam under surveillance." Expert Committee on Drug Dependence, World Health Organization, Thirty-second Report 14 (2001). In this case, however, WHO did not interpret "surveillance" to mean "put diazepam on the agenda again," and diazepam was <u>not</u> on the agenda of the 2002 ECDD.

There is no justification to put tramadol on the agenda for critical review at the March 2006 ECDD meeting.

The amount of time allowed to provide a response to WHO's questionnaire was palpably inadequate. These data have been assembled under very difficult circumstances, in the period between December 13, 2005 and January 12, 2006. The haste to call an ECDD meeting has imposed, on those who would comply, the need to collect the answers to the questionnaire during the prime holiday season in the United States and much of the rest of the world. As long ago as 1992, the ECDD recognized that "[a]dequate time should ... be allowed for the Secretariat to

notify interested parties and collect their comments." Expert Committee on Drug Dependence, World Health Organization, Twenty-eighth Report 37 (1993). That has not occurred here, and the only stated justification for the need for haste is that the agency could not hold the meeting in a timely fashion "... owing to internal limitations." Lepakhin supra. The need to call an urgent meeting, to cure the problem caused by "internal limitations," should not be permitted to have a greater priority than the need for time to prepare a presentation of relevant data.

Our government should object to WHO's actions, which violate the agency's own rules and will cause the next ECDD to make important medical judgments without the benefit of a complete presentation of all relevant data.

II. UPDATE ON ABUSE RISK FOR TRAMADOL

SUMMARY

Tramadol is a synthetic analgesic with weak μ-opioid and non-opioid effects. Two complementary mechanisms appear applicable: weak binding to μ-opioid receptors and weak inhibition of reuptake of norepinephrine (NA) and serotonin (5HT). Tramadol's dual mechanism of action differentiates it from prototypic opioids such as morphine or codeine. The dual mechanism of action may explain the weak opioid side effect profile and low abuse liability of tramadol.

A 1992 expert report on the abuse liability of tramadol from the Center of the Chemical Dependence of Medicine in Baltimore, Maryland, concluded that the abuse potential of tramadol is low for four basic reasons: i) the low potency to produce opioid-like subjective effects and euphoria with respect to its analgesic potency; ii) the non-opioid component of tramadol is not related with psychotropic or reinforcing effects; iii) 300 mg intramuscular doses in post-addicts were not euphorigenic; and iv) the delayed onset of action in comparison with prototypic opioids.

The abuse risk of tramadol has been extensively investigated utilizing data from epidemiological and post-marketing surveillance studies, including the WHO Collaborating Centre for International Drug Monitoring, the Grünenthal Worldwide Spontaneous Reporting Database, a post-marketing

surveillance programme on tramadol abuse (ISC) in the USA, the Drug Abuse Warning Network (DAWN) in the USA, the Substance Abuse Warning System (SAWS) in Germany, the Toxic Exposure Surveillance System (TESS), and the National Forensic Laboratory Information System (NFLIS).

Tramadol's abuse risk has not increased since 1992. In contrast, the relative frequency of tramadol abuse (i.e. number of abuse reports versus sales) is in the same range in 2005 as it was in 1992, when the WHO assessed that no significant abuse had been reported. This is consistently confirmed by the available, evidence-based epidemiological data.

Since the recent critical review in 2002, there have been no changes in the rate of abuse of tramadol which remains stable at 0.5 reports per million DDD. The increase of abuse reports from 2002 to 2005 reflects a substantial increase in patient exposure without a corresponding increase of abuse.

The available evidence establishes that tramadol does not present a risk to public health or a significant potential for abuse. Twenty-eight years of experience have demonstrated the therapeutic usefulness of tramadol for treatment of moderate to severe pain. As an effective analgesic with demonstrated low rates of abuse and dependence, the non-controlled availability of tramadol as a regular prescription-only drug has proven to be of considerable benefit to millions of individuals who might otherwise suffer with inadequately treated pain.

1. Introduction

Millions of individuals are affected by acute or chronic pain. According to a World Health Organization (WHO) survey of more than 20,000 primary care patients observed across five continents, over 20% had suffered from persistent pain.[1] Despite recent worldwide efforts to increase recognition and appropriate treatment of pain, and the increasing familiarity with the concept of the WHO Analgesic Ladder, pain continues to be a significant worldwide health issue. There are many factors that lead to the continued inadequate management of pain, including

inadequate treatment by clinicians with insufficient knowledge of pain assessment and therapy, inappropriate concerns regarding analgesic side effects and fear of addiction, a tendency to give lower priority to symptom control than to disease management, and patients' underreporting of pain and noncompliance with analgesic therapy.

Tramadol was first introduced in 1977 and is available in over 100 countries today. It is widely used for the treatment of moderate to moderately-severe or severe pain. WHO concluded in 1992 that tramadol had rarely been associated with the development of tolerance and no significant abuse had been reported. Tramadol was not recommended by the WHO committee for critical review "on the basis of its low abuse liability."[2] A critical review in 2002[3] by a WHO Expert Committee on Drug Dependence (ECDD) determined that "the information available was not sufficient to recommend international control of tramadol, but is adequate to recommend that WHO keep the drug under surveillance."[4]

Tramadol is currently not subject to international control under either the 1961 or the 1971 Conventions. At present, WHO is critically reviewing tramadol's abuse risk to determine whether international control of the drug is necessary, despite the fact that it had been reviewed at the last ECDD meeting.

The critical review will determine whether the abuse risk of tramadol has changed since the 1992 WHO pre-review and the 2002 critical review to see if it constitutes a significant public health risk.

In this document, tramadol's mechanism of action, availability, and therapeutic use are briefly described, followed by data on its abuse risk. Worldwide information available at the date of this report includes: data from the WHO International Drug Monitoring Programme, the Grünenthal Worldwide Spontaneous Reporting Database, several surveillance programs, and data from the scientific literature. Collectively, this body of data further demonstrates the low abuse of tramadol and affirms both the 1992 and 2002 decisions of the WHO ECDD not to place tramadol under international control.

2. Mechanism of Action

Tramadol exists as a racemic mixture of two isomers. Tramadol's dual mechanism of action distinguishes it from prototypic μ-opioid analgesics such as morphine or codeine. The analgesic action of tramadol combines opioid and non-opioid components, i.e. a weak activity at the μ-opioid receptor and a weak inhibition of noradrenaline and serotonin reuptake.[1]

2.1 Receptor Binding

Opioid receptor

The μ-opioid receptor affinity of tramadol is approximately 5-10 times lower than the affinity of codeine. Tramadol's opioid properties are predominantly attributed to the (+)-enantiomer of the metabolite O-desmethyltramadol (M1). The μ-opioid receptor affinity of tramadol's metabolite M1 is 10-100 times lower than that of morphine;[2,3] morphine is the active metabolite of codeine. The lower opioid receptor affinity of both the parent compound and the active metabolite as compared to codeine may explain the relatively weak opioid side-effect profile of tramadol.

Table 1: Opioid receptor affinity and inhibition of monoamine uptake of tramadol, its M1-metabolite, enantiomers and reference compounds[3]

Compound	μ[a]	NA	5-HT
Tramadol	8.3	1.8	1.9
(+)-Tramadol	4.4	6.9	0.87
(-)-Tramadol	130	0.59	4.8
Tramadol metabolite			
(+)-M1	0.017	42	7.5
Codeine	1.3	>100	>100
Morphine	0.0022	>100	>100
Nisoxetine	--	0.0017	0.37
Fluoxetine	-	0.53	0.026

[a] values are Ki in μM, **lower values denote higher pharmacological action**

NA=noradrenaline; 5-HT=5-hydroxy-tryptamine (serotonin); μ=μ-opioid receptor

Monoamine re-uptake inhibition

Tramadol differs from prototypic opioids because its non-opioid mechanism, related to the uptake inhibition of the neurotransmitters noradrenaline (NA) and serotonin (5HT), also contributes to its analgesic effect. NA-uptake inhibition is most prominent in the (-)-enantiomer, and 5HT-uptake inhibition occurs in the (+)-enantiomer of tramadol, thus showing that both enantiomers contribute to the analgesic properties of racemic tramadol.

2.2 Atypical mechanism of action

Studies in animal pain models have confirmed that the antinociceptive properties of tramadol involve a combination of its opioid and non-opioid mechanisms of action.[1,4-6] Comparable findings have been shown in healthy volunteers.[7,8]

Clinical studies found that the metabolite M1 is only partially responsible for the overall analgesic effect of tramadol. The parent compound, tramadol, is analgesically active and therefore is not considered to be a mere prodrug.[7,9,10] This differentiates tramadol from codeine, since codeine's analgesic effect is essentially mediated by morphine formed via metabolism of codeine.

2.3 Conclusion

Tramadol is a synthetic analgesic with weak μ-opioid and non-opioid effects, related to the uptake inhibition of the neurotransmitters noradrenaline and serotonin. Its dual mechanism of action differentiates it from prototypic opioids such as morphine or codeine.

Tramadol is not a mere pro-drug since the metabolite M1 (μ-opioid component) is only partially responsible for tramadol's analgesia. The parent compound tramadol is itself an analgesic.

These unique pharmacological properties may explain both the significantly low abuse and the unique adverse event profile of tramadol.

Tramadol is not convertible or metabolized to a drug under international control.

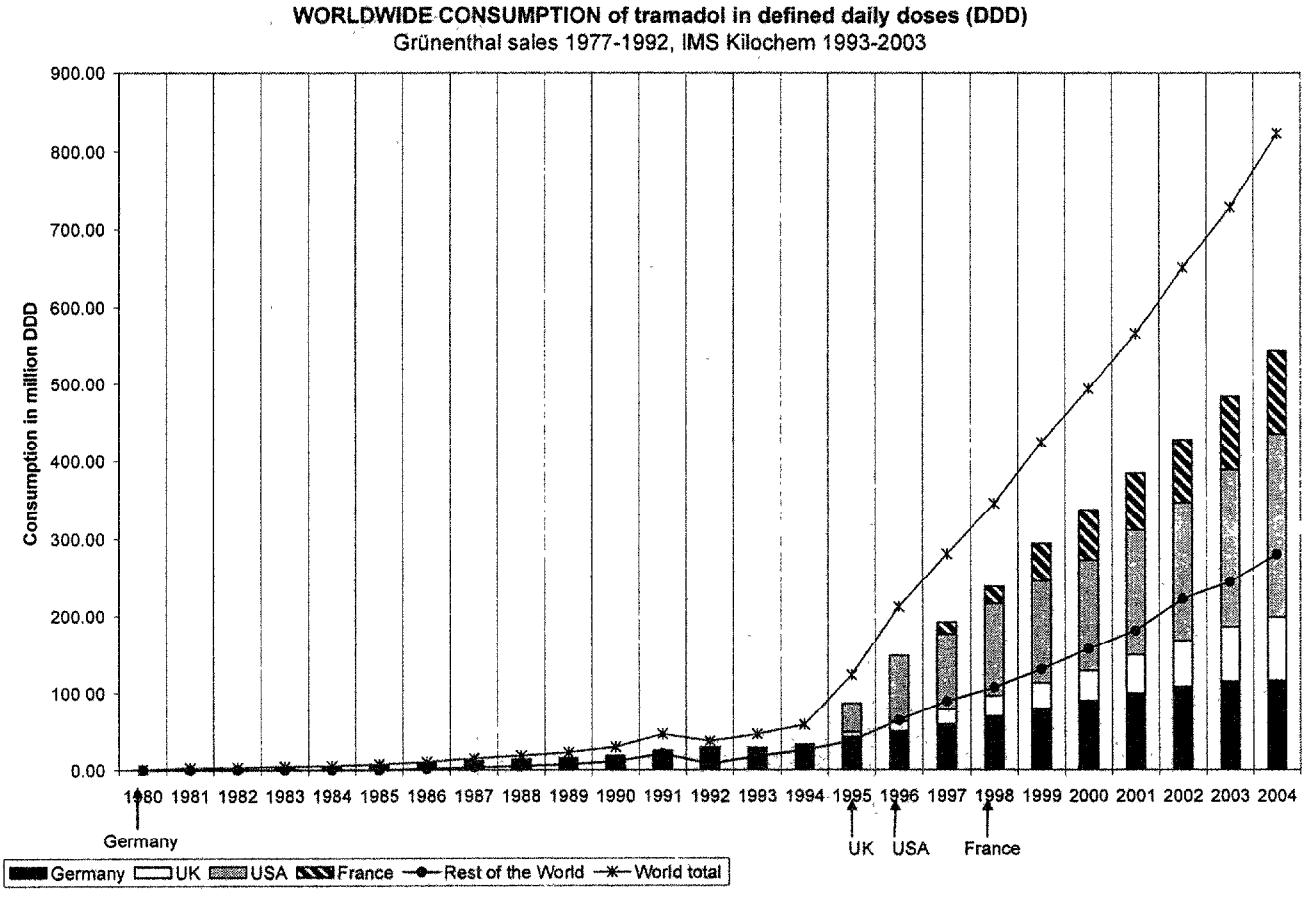
3. Availability and Consumption

Tramadol was developed by Grünenthal and was first registered in Germany in 1977 as a parenteral formulation. It is now available in more than 100 countries in the following formulations: solution for injection 50 and 100 mg, 100 mg suppositories, 50 mg immediate-release capsules or tablets and drops. Oral formulations have been available since 1980. After 1994, sustained-release tablets in different dose strengths were approved for use.

Data on the number of patients' prescriptions are not available in Germany and most other European countries. Therefore, the increase in patient exposure is presented using total sales and consumption data (IMS-KG Kilochem Data). The patient exposure is estimated using a daily dose of 300 mg, as defined by the WHO, and a standard treatment duration of 28 days (Grünenthal Product Safety Update Reports). Since 1977, over 1,486,060 kg of tramadol have been sold, and an estimated 176 million patients have been exposed to tramadol worldwide. Between 2001 and 2004, there was a 46% increase in patient treatment days from 656 million to 823 million (Figure 1).

From 1992 to 2005, worldwide availability increased from approximately 60 to more than 100 countries. Between 1993 and 2004, global sales of tramadol increased 17-fold, i.e. from 13,842 kg in 1993 to 247 kg in 2004.[1] Consumption rose to a worldwide total of 823 million defined daily doses (DDD= 300 mg) of tramadol (Figure 1). The launch of tramadol in major Western European countries and the USA between 1994 and 1997 played a major part in the overall increase of sales.

Figure 2:


WORLDWIDE CONSUMPTION of tramadol in defined daily doses (DDD)
Grünenthal sales 1977-1992, IMS Kilochem 1993-2003
Consumption in million DDD
900.00
800.00
700.00
600.00
500.00
400.00
300.00
200.00
100.00
0.00
1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
Germany
UK
USA
France
Germany
UK
USA
France
Rest of the World
World total

4. Clinical Utility

Tramadol is registered for the treatment of moderate to moderately-severe or severe pain; it is used parenterally (i.m., i.v., s.c.), orally or rectally.

Recommended tramadol doses are 50 to 100 mg single dose and up to a daily dose of 400 mg. According to data from a late 1990s post-marketing surveillance, the average daily dose of tramadol in practice is around 200 mg per day.[1-3]

Tramadol is suitable in cases that would call for initial treatment with opioids after NSAIDs or when acetaminophen alone has failed because of insufficient analgesia or contra-indications. Its efficacy overlaps with lower doses of morphine.

4.1 Clinical efficacy

Twenty-eight years of experience have demonstrated tramadol's therapeutic usefulness in almost all types of moderate to moderately-severe or severe pain. Selected clinical studies are briefly summarized below:

Postoperative pain

Tramadol has been investigated in postoperative pain, intraoperative analgesia and day surgery. Tramadol provided similar efficacy as compared to morphine with a potency ratio of about 1:11-12 when administered postoperatively i.m. and/or i.v.[4,5] In addition, tramadol demonstrated similar analgesia to that of several NSAIDs including ketorolac, naproxen or dipyrone and clonixin.[6] Intraoperative tramadol showed analgesia similar to equipotent doses of morphine.[7-9] In studies on the use with tramadol in day surgery, intravenous and oral tramadol provided better analgesia than intravenous fentanyl with oral codeine and acetaminophen or ketorolac.[10,11] Tramadol was associated with a lower incidence of respiratory depression as compared to traditional opioids such as morphine. Compared to NSAIDs, it lacks gastrointestinal or renal toxicity.

Obstetric pain

In parenteral obstetric pain studies, tramadol was compared to pethidine and showed similar efficacy.[12-15] Effects on the respiratory rate in the neonates were less than with pethidine in two studies.

Acute trauma pain and emergencies

An open-label, randomised study comparing oral tramadol and diclofenac showed better efficacy for tramadol.[16] An open study in 142 patients with tramadol i.v. concluded that it can be administered safely and effectively by non-physicians or paramedical personnel in a prehospital situation.[17]

Cancer pain

Double-blind studies in cancer pain showed that oral tramadol is as effective as low dose morphine.[18,19] An open study of high-dose tramadol vs. low dose morphine in cancer pain demonstrated similar pain intensity ratings in both groups, but more constipation, neuro-psychological symptoms and pruritus in the morphine group.[20]

In the 2nd edition of Cancer Pain Relief 1996 by the WHO,[21] tramadol is mentioned as an alternative to opioids for the treatment of moderate to severe pain, causing less constipation and respiratory depression than prototypic opioids at equianalgesic doses.

Osteoarthritic pain

In order to demonstrate efficacy in patients in whom NSAIDs are contraindicated or failed, two recent double-blind studies in osteoarthritis compared tramadol to placebo with an underlying NSAID baseline treatment or to diclofenac.[22,23] Both studies showed efficacy of tramadol and an individual response between tramadol and diclofenac. In addition to analgesia, function ability was improved. A double-blind study by Schnitzer et al in 1999 showed that in naproxen responders, the addition of tramadol allows reduction of the naproxen dose without affecting pain relief.[24]

The IASP Special Interest Group on Rheumatic Pain (IASP SIG) and the American College of Rheumatology (ACR) suggest tramadol for the treatment of osteoarthritic pain of the hip and knee when acetaminophen and NSAIDs are not effective enough or contraindicated.[25,26]

Low back pain

Two double-blind studies in low back pain (tramadol vs. placebo, tramadol capsules vs. tramadol sustained release tablets) indicate that patients with persistent low back pain and insufficient response to peripheral analgesics can benefit from treatment with tramadol.[27,28]

Paediatric pain

Most of the studies in children used the parenteral dosage form, either i.m. or i.v. in doses below 1 mg/kg/bodyweight to 2.5 mg/kg/bodyweight. Five double-blind trials in various post-surgical pain syndromes showed that tramadol is effective and safe, efficacy being comparable to pethidine, nalbuphine or fentanyl with less effects on respiratory function.[29-33]

In several countries, tramadol is licensed for paediatric use as solution for injection and drops.

Neuropathic pain

Tramadol's dual mechanism of action prompted investigation in neuropathic pain, which is difficult to treat with available drugs. Three studies, an open pilot study versus clomipramine/levomepromazine, a placebo-controlled seven week study in patients with long standing diabetic neuropathic pain and an 8-week placebo controlled study in painful persistent polyneuropathy show that tramadol can be a useful therapeutic alternative for pain relief in neuropathic pain.[34-36]

Other pain states

Other pain states investigated included for example dental surgery pain,[37] pancreatic pain,[38] ureteral colic[39] or fibromyalgia pain.[40,41]

4.2 Safety profile

Common adverse events that can occur following tramadol administration include dizziness, nausea, vomiting, headache, somnolence, dry mouth, constipation and sweating (Grünenthal core data sheet).

Spontaneous reports on adverse events indicate that tramadol may be endowed with a certain risk to induce seizures.[42,43] As identified from these reports, the main risk factors have been overdoses, a history of seizures or patients taking seizure-threshold reducing agents.

In normal patients and in the absence of proconvulsant co-medication, the seizure risk of therapeutic dosages is low and case control studies in very large populations indicate that the seizure risk is not increased as compared to other pain medications.[44-46]

The low dependence potential of tramadol is mentioned in the Summary of Product Characteristics and attention is drawn to the need for careful supervision when tramadol is used in patients with a tendency for drug abuse (Grünenthal core data sheet). The number of adverse events related to abuse liability was small in clinical trials, supporting a low abuse potential for tramadol.

Compared to prototypic opioids, clinical studies with tramadol demonstrate fewer effects on the cardiovascular system,[47] respiratory function,[48-51] immuno-supression,[52] gastrointestinal motor function[53,54] and contraction of gastrointestinal sphincters.[55]

Recent case studies have discussed serotonin syndrome in which drug interaction with other serotonergic agents causes symptoms such as increased blood pressure, headache, and agitation. The presence of serotonin syndrome is related to tramadol's dual mechanism of action. The case reports from literature have all been documented in the Grünenthal Drug Safety Database.

4.3 Recent reviews

A worldwide literature search done on December 22, 2005 produced additional studies from around the world that reinforce tramadol's therapeutic value. A review was published by Scott & Perry on the use of tramadol in perioperative pain.[56] The authors concluded that:
"*tramadol has no clinically relevant effect on respiratory or cardiovascular parameters. Tramadol may prove particularly useful in patients with poor cardiopulmonary function, including the elderly, the*

obese and smokers, in patients with impaired hepatic or renal function and in patients in whom nonsteroidal antiinflammatory drugs are not recommended or need to be used with caution...." (p. 141)

The clinical use of tramadol in acute and non-acute pain has been reviewed in a publication by Bamigade & Langford in 1998.[57] The authors concluded:

"The blend of efficacy, multiple formulations and a low potential for serious adverse effect at higher doses or in prolonged therapy, provide tramadol with a useful profile for both short- and long-term use in hospitals and in the community.... In cancer pain it can provide satisfactory analgesia for moderately severe levels of pain with maintenance of good activity and quality of life, but it is demonstrably inferior to morphine for the treatment of severe pain" (p. 178.)

4.4 Conclusion

Tramadol has demonstrated therapeutic usefulness in the treatment of moderate to moderately-severe or severe pain, e.g. in postoperative and post-traumatic pain, cancer pain, and pain associated with chronic benign diseases. Tramadol's efficacy overlaps with low doses of morphine.

Classical side effects of morphine-like drugs such as constipation, respiratory depression and sedation are reduced with tramadol.

Thus, tramadol is an effective and safe drug for the treatment of pain. As such, tramadol is a unique tool for filling the analgesic gap that exists between NSAIDs and potent prototypic opioids.

5. Abuse Liability

In 1992 and 2002, the ECDD reviewed the preclinical and clinical abuse liability data and came to the conclusion that tramadol had a low abuse liability. The following section summarises the conclusions from earlier studies and highlights newer studies. Preclinical studies on the abuse potential, tolerance and withdrawal properties of tramadol were conducted in various models in mice, rats and primates. Comparators included opioids such as codeine, pentazocine, nalbuphine and morphine.

5.1 Abuse liability in preclinical animal studies

Based on a series of studies in monkeys, Yanagita demonstrated that tramadol had limited reinforcement potential compared to pentazocine and codeine.[1] The weak μ-opioid properties of tramadol were confirmed in a drug discrimination test in morphine-trained rats. The study demonstrates that high doses of tramadol were required to substitute for low-dose morphine in morphine-trained rats.[2]

Tolerance and withdrawal

Tolerance in the mouse and the rat is not significant[3] and lower than with morphine.[4] Unlike the tolerance exhibited with morphine, nalbuphine, and buprenorphine, Kayser et al demonstrated that tramadol showed no tolerance in the normal and arthritic rat.[5]

Tramadol proved inadequate in treating withdrawal syndrome in the rat and the monkey.[1,6] Physical dependence assessed in the mouse, the rat and the monkey was moderate and less than that of morphine, pentazocine and codeine.[3,4,7]

A recent study performed in mice was carried out with tramadol to investigate the antinociceptive activity and the potential ability to develop tolerance, cross-tolerance and/or physical dependence in comparison to morphine. Contrary to morphine, tramadol did not induce tolerance and tramadol pretreated animals did not show withdrawal signs after the administration of naloxone.[8]

Expert report

The physical dependence potential of tramadol has been reviewed in an expert report from the University of Minnesota.[9] The report concluded that tramadol appears to be an analgesic with minimal liability of tolerance and physical dependence.

5.2 Abuse liability in human clinical studies

Clinical trials investigating tramadol's abuse liability, physical dependence and tolerance were conducted in a variety of subject populations including healthy volunteers, subjects with chronic pain, and opiate addicts (Appendix 2). Subjects were evaluated for subjective, behavioral and psychophysiological responses; withdrawal symptoms; the ability to mitigate withdrawal symptoms; tolerance and psychomotor responses after tramadol administration for up to 2 years. In controlled studies, placebo was used as a negative control; tilidine/naloxone, morphine or oxycodone were used as positive controls in studies investigating subjective, behavioural and psychological effects.

Abuse potential

Healthy volunteers

Two studies of healthy volunteers demonstrated that tramadol (100 mg im, oral drops) did not have any euphoric or dysphoric effect when compared to placebo.[10,11]

Opiate addicts

Tramadol did not differ from placebo at doses of 75 mg and 150 mg in a double-blind, cross-over trial in 12 former drug addicts,[12] but was identified as being an opioid at the dose of 300 mg. However, even at this dose the drug was not rated as likeable and did not produce other opioid effects. In another study,[13] very high single oral doses of tramadol were used (175, 350 and 700 mg) in opiate abusers in comparison to oxycodone (20 and 40 mg) and placebo. Tramadol 700 mg (7 times the recommended single therapeutic dose) and oxycodone 40 mg produced similar opiate-like effects. The miotic response was less for tramadol, which also, in contrast to oxycodone, raised blood pressure earlier and to a greater extent, suggesting multiple mechanisms of action and a weaker opioid-like activity for this very high dose of tramadol.

Tramadol (100 mg and 300 mg) did not differ from placebo with regard to subjective and objective effects in a study in 6 addicts maintained on the same dose of methadone.[14]

A 1999 Chinese study by Liu et al found a mild degree of physical dependence in 142 cases in an undetermined population of 219 opiate addicts with a history of tramadol abuse.[15] Thirty-five percent of the population experienced no withdrawal when terminated from use of tramadol. The remaining cases had mild withdrawal based on average scores lower than 1 on a scale of 0-4 where 0 was none and 1 was mild.

These studies show that even high doses of tramadol induce few subjective effects, even in post-addicts who are particularly able to identify them.

Tolerance and withdrawal

A series of non-comparative, long-term studies measured tolerance by monitoring dosing levels over time and included an assessment of withdrawal symptoms at the end of the trial period using a naloxone precipitation test. The doses remained constant suggesting no evidence of tolerance and only mild to marginal withdrawal.[16-18]

Three chronic pain studies (n=820) conducted over 1 – 3 months[19-21] did not show any reduction in the analgesic effect of tramadol over time, nor a significant increase in drug consumption at normal therapeutic doses.

Expert report

A 1992 expert report on the abuse liability of tramadol[22] from the Center of the Chemical Dependence of Medicine, in Baltimore, Maryland, concluded that the abuse potential of tramadol is low for four basic reasons: i) the low potency to produce opioid-like subjective effects and euphoria with respect to its analgesic potency; ii) the non-opioid component of tramadol is not related with psychotropic or reinforcing effects; iii) 300 mg intramuscular doses in post-addicts were not euphorigenic; and iv) the delayed onset of action in comparison with prototypic opioids.

5.3 Conclusion

The collective data in animal and human studies conclusively demonstrate the low abuse liability of tramadol. The data indicate that the risk for development of tolerance and psychological or physical dependence with tramadol is low.

Compared to morphine, tramadol did not exhibit tolerance and withdrawal was mild to moderate.

Results from postmarketing surveillance studies demonstrate tramadol's relatively low abuse liability consistent with the findings of the WHO 2002 critical review. The expanded body of data does not change the assessment.

6. Abuse Risk: Epidemiological Data and Case Reports

The FDA's "Draft Guidelines for Abuse Liability Assessment," based on the Drug Abuse Advisory Committee Meeting of the FDA in July 1990, acknowledged that epidemiological data, when available and of good quality, can be a good indicator of abuse potential. The epidemiological data available for tramadol span the course of 28 years.

Several sources of epidemiological data for tramadol exist: WHO Collaborating Centre for International Drug Monitoring, Grünenthal Worldwide Spontaneous Reporting Database, a post-marketing surveillance programme on tramadol abuse (ISC) in the USA, the Drug Abuse Warning Network (DAWN) in the USA, the Substance Abuse Warning System (SAWS) in Germany, Toxic Exposure Surveillance System (TESS), and the National Forensic Laboratory Information System (NFLIS).

Accurate definitions relating to dependence, abuse, withdrawal, and tolerance are necessary for a scientific analysis of abuse and public health risk. Thus harmonization efforts by WHO, ICD-10™ and Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV™) groups have led to the recognition that abuse/harmful use is characterized by use despite harm and that drug dependence (addiction) is characterized by loss of control (Appendix 1). Appendix 1 also contains a consensus statement of recommended definitions from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine representing current practice in the US. It is important to distinguish between physical dependence or withdrawal effects and drug abuse/harmful use. Withdrawal syndrome and tolerance are physiological adaptations and are not by themselves sufficient to define dependence. Withdrawal is a time-limited symptom that occurs at discontinuation of continuous exposure to medication. It can occur with medications with almost no abuse potential, eg anti-hypertensives, tri-cyclic antidepressants, and steroids.

6.1 International adverse event reporting databases

The adverse events relating to abuse liability are withdrawal, depersonalization, cognitive dysfunction, hallucinations, euphoria, depression, and cognitive dysfunction. The number of adverse events related to abuse liability was small in clinical trials, supporting a low abuse potential for tramadol. However, it is prudent to monitor abuse rates when over 90 million people have been exposed to tramadol.

WHO International Drug Monitoring Programme

The WHO International Drug Monitoring Programme was established in 1968. At present, 78 countries are official members and 14 are associate members in the programme. The WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from participating countries. Reports submitted to this system come from both regulatory and voluntary sources. Some National Centres accept reports only from medical practitioners, others accept reports from a wider spectrum of health professionals and some National Centres also submit reports from pharmaceutical companies. Due to the variability in reporting, the following caveats should be noted.

Caveat: The reports are not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction, and no information is provided on the number of patients receiving the products for which reports are received. Also, the volume of reports may be influenced by the extent of use of the product, publicity, and other factors that vary by product to product and by country to country. The information in the reports does not represent the opinion of the World Health Organization [excerpted from *"Accompanying statement to data released from the WHO Collaborating Centre"*].

Tramadol has been available since 1977. Through the 3rd quarter of 2005, the WHO database contains 1,705 symptoms or 3.4 symptoms per one million patient days of exposure. This yields a rate of 5.9 symptoms per 1 million patient days of exposure. In 2004, the WHO database contains 1,391 symptoms or 5.6 symptoms per one million patient days of exposure.

Table 2. Cumulative number of tramadol symptoms/reports relating to dependence, abuse or withdrawal (WHO-ART codes 0174, 0175, 0200, 0898): data excerpt from the WHO International Drug Monitoring Programme, through 3rd quarter 2005.

WHO International Drug Monitoring Programme

	USA	Germany	France	UK	Switzerland	Belgium	Denmark	Austria	Sweden	Finland	Jordan	Norway	Australia	Chile	Ireland	Lebanon	Netherlands	Rest of world	Total
Year of launch	95	77	97	94	82	94	93	84	95	95	95	98	98	92	95	85	93	n.a.	n.a
symptoms relating to:																			
- drug abuse	332	11	-	3	1	-	1	-	-	-	-	-	-	-	-	-	-	-	348
- drug dependence	556	23	-	32	2	6	7	-	31	-	-	-	3	1	-	-	-	2	663
- withdrawal	429	20	1	134	6	1	8	1	29	-	-	-	39	1	2	-	11	12	694
No. of reports	1059	50	1	158	8	7	16	1	51	-	-	-	40	2	2	-	11	14	1420
No. of reports	1059	50	1	158	8	7	16	1	51	-	-	-	40	2	2	-	11	14	1420

The data are mostly from the US (75%) and to a lesser extent from the United Kingdom and Germany

The increase in the number of reports in the WHO database on tramadol abuse/dependence and withdrawal after 1992 reflects the launch of tramadol in additional countries, especially in major markets such as the USA (tramadol launch in 1995) and the UK (tramadol launch in 1994).

Of the 1,705 symptoms reported, 694 were related to withdrawal syndrome without abuse, while 663 related to drug dependence and 348 to drug abuse. As noted before, withdrawal in the absence of other drug seeking behaviours does not represent abuse in any of the ICD-10™, DSM-IV™ or WHO definitions (Appendix 1). Furthermore, relative to over 178 million patients who have been successfully treated with tramadol since 1977, this represents a small number of symptoms (approximately 2 per one million patient days) associated with abuse and dependence.

It has to be further noted that when considering the data, the symptoms reported should not be treated cumulatively because reports often mention multiple symptoms (e.g., drug abuse + drug dependence + withdrawal, etc). This can lead to "case multiplication" in symptom listings. For example, the 1,317 symptoms reported from the US relate to 1,059 reports.

As shown above, the source of most of the symptoms found in the WHO database is the United States after tramadol was launched in 1995. Data from the ISC proactive postmarketing surveillance program on tramadol abuse/dependence are available for an accurate evaluation of the symptom accumulation in the WHO database.

Grünenthal Worldwide Spontaneous Reporting Database

Tramadol is marketed in more than 100 countries. Adverse event reports on tramadol have been collected worldwide since 1977 by the Corporate Drug Safety at Grünenthal. Reports are generated by health professionals or consumers. Case reports from the literature and solicited reports are also included in this database.

As of December 31, 2004 the Grünenthal database contains 1,593 reports on tramadol related to dependence/abuse and 778 reports on tramadol related to withdrawal, exclusively (without abuse/dependence) (Table 3).

Table 3. Cumulative number of tramadol symptoms/reports relating to dependence, abuse (MedDRA Proferred Terms (PT) version 8.0: Dependence, Drug dependence, Drug abuser, Intentional misuse, Polysubstance abuse, Polysubstance dependence and Delirium tremens) or withdrawal (MedDRA Perferred Terms (PT) version 8.0: Withdrawal syndrome, Drug withdrawal convulsions, Drug withdrawal headache, Drug withdrawal maintenance therapy): data excerpt from the Grünenthal Worldwide Spontaneous Reporting database, December 22, 2005.

Grünenthal Corporate Drug Safety Database

	USA	Germany	UK	France	Sweden	Denmark	Austria	Belgium	Switzerland	Netherlands	Chile	Jordan	Ireland	Spain	Finland	Lebanon	Norway	Australia	Canada	TOTAL
Year of drug launch	'95	'77	'94	'97	'95	'93	'84	'94	'82	'93	'92	'95	'95	'92	'95	'85	'98	'98	-	
Symptoms relating to	1268	313	124	82	13	9	7	6	6	5	4	4	3	3	2	2	2	1	1	1855
- Drug dependence	320	212	22	10	1	5	4	4	4	1	1	1	1	-	-	2	2	-	-	590
- Drug abuse	446	57	2	2	1	-	1	1	1	-	1	1	-	-	1	-	-	-	-	514
- Withdrawal syndrome	502	44	100	70	11	4	2	1	1	4	2	2	2	3	1	-	-	1	1	751
No of reports	1017	297	114	75	12	9	5	6	5	5	2	2	2	3	1	1	2	1	1	1560

Comparable to the WHO database, the majority of the reported symptoms came from the USA (75%) followed by Germany, France and UK.

Since the initial launch of tramadol in 1977 until the end of 2004, there have been 778 case reports in the Grünenthal database concerning withdrawal symptoms without any drug-seeking behaviour. Cases with withdrawal symptoms only are not included since withdrawal by itself is not sufficient to define dependence or abuse/harmful use (DSM-IV-TR criteria, 28th ECDD meeting).

The increase of reports from 1992 to 2004 reflects the launch of the drug in new markets and the substantial increase in patient exposure and is not an increase of abuse. Figure 2 shows the number of abuse/dependence reports in relation to patient exposure. It should be noted that cases of withdrawal in the absence of drug-seeking behaviour are not included since they are not related to abuse as defined by ICD-10, DSM-IV, WHO definitions and the Consensus Statement on Definitions Related to the Use of Opioids. Reporting rates were calculated as the ratio of number of reports in the Grünenthal database per

1 million defined daily doses of tramadol (DDD = 300 mg) sold. Sales data for 1993 - 2004 were derived from the IMS Kilochem statistics and from Grünenthal sales statistics before 1993.

Figure 2:

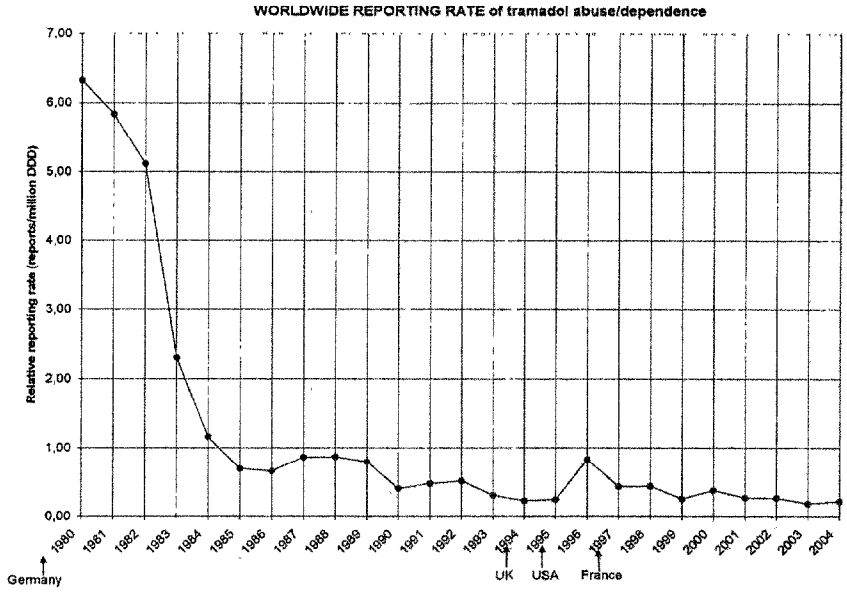
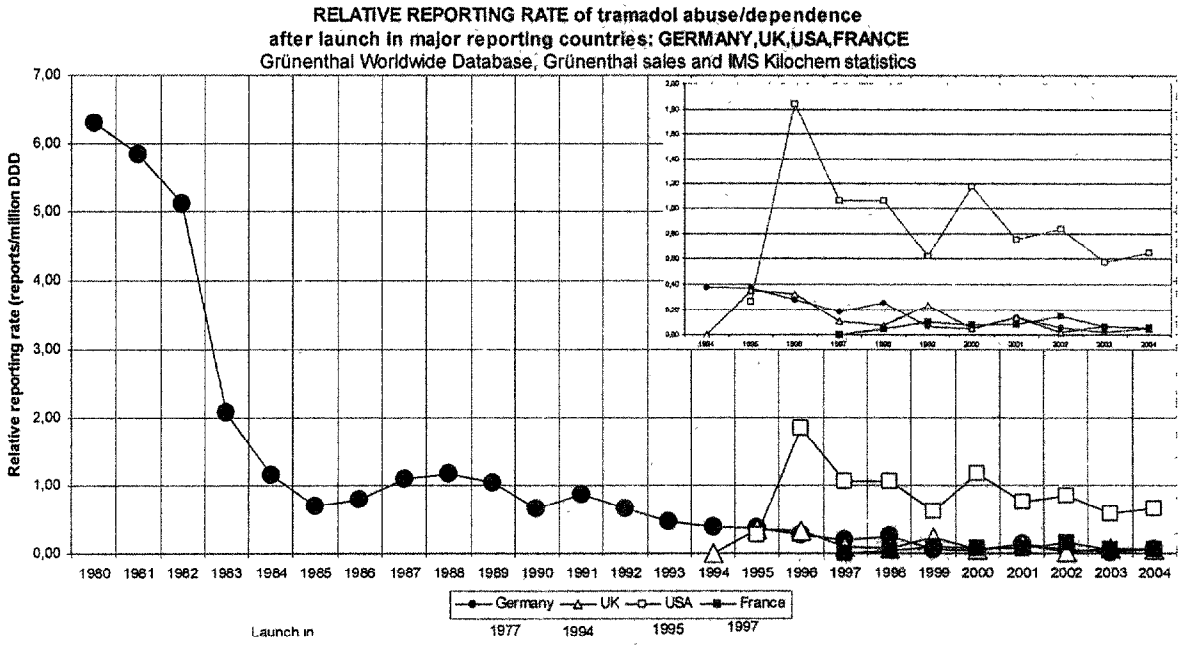


Figure 3:



In relation to patient exposure, reporting rates have decreased over time. The relative frequency of tramadol reports on abuse/dependence in the USA, UK and France is comparable to that of Germany during the first few years on the market and in a range that was rated not significant by the WHO in both the 1992 and 2002 reviews.

Caveat: It should be noted that the data from the three databases overlap: WHO International Drug Monitoring Programme, Grünenthal Worldwide Spontaneous Reporting Database, and the US Independent Steering Committee data (Section 6.3).

Conclusion

When adjusted for the increased consumption, the relative frequency of tramadol reports on abuse/dependence and withdrawal has decreased. Thus, although the total number of reports on abuse/dependence/withdrawal gathered by the WHO International Drug Monitoring Programme and by Grünenthal has increased considerably since the two WHO reviews in 1992 and 2002. However, the increase of reports seen in both databases reflects the substantial increase of tramadol sales since then and is not an increase of abuse. The USA, where tramadol was launched in 1995, contributed to the majority of the reports. It should be noted that proactively collected reports from the Independent Steering Committee (ISC) in the US are included in the Grünenthal database (for detailed description see chapter 6.3).

6.2 Central nervous system stimulation or depression

A separate analysis examined terms associated with specific CNS terms using the data from Uppsala. For the period from 1977 to 3 July 2001, the WHO Drug Monitoring Database contains 97 reports on tramadol and euphoria; this relates to over 90 million patients treated with tramadol in the same period.

Examination of adverse events was conducted in four postmarketing surveillance studies in Europe[1-4] and three in the US.[5-7] In the 14,932 patients examined, 7,532 adverse events were reported.[8] Of the adverse events reported, 142 (1.8%) referred to central nervous effects, including withdrawal, abnormal dreaming,

cognitive dysfunction, difficulty concentrating, depersonalization, depression, euphoria, or hallucinations. Depression/dysphoria accounted for 60 of the 7,532 total adverse events (0.8%). Euphoria and hallucinations (including visual and hearing disturbances) accounted for only 20 (0.26%) of the total adverse events reported in these 7 studies.

Again, considering the worldwide exposure of tramadol, this is a remarkably small number of events.

6.3 Post-marketing surveillance programme on tramadol abuse in the USA

Background

Tramadol 50 mg immediate release tablets, which are marketed as Ultram® by Ortho-McNeil Pharmaceutical (OMP) in the USA, were approved by the US Food and Drug Administration (FDA) in April 1995 for the treatment of moderate to moderately-severe pain. Based on the recommendation of the FDA's Drug Abuse Advisory Committee (DAAC) in 1994, tramadol was classified as a prescription-only drug but not scheduled under the US Controlled Substances Act (CSA). This approval was contingent upon the development of a proactive surveillance programme to detect any signs that tramadol abuse might be emerging, particularly in populations at risk for abuse.

An Independent Steering Committee (ISC) was formed upon request from the FDA and with the support of the licensee for tramadol in the US, Ortho-McNeil Pharmaceutical, to develop a comprehensive, proactive post-marketing surveillance programme and two analytical studies.[9] The ISC panel was comprised of eight US abuse experts.

Description of the surveillance programme

The Independent Steering Committee developed a two-tiered approach to detect whether tramadol has a significant abuse risk:

I) A comprehensive proactive surveillance programme

The Independent Steering Committee proactively monitors reports of tramadol abuse from a variety of sources including:

- Spontaneous reports of abuse (MedWatch)
- Key informant network, i.e.:
  - 110 grantees of the National Institute on Drug Abuse (NIDA)
  - 145 drug abuse experts (e.g. treatment counselors, methadone clinical directors)
- Internet links to addict chat groups
- Diversion study

Reports from all these sources were documented and assessed by the Independent Steering Committee according to criteria contained in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV™) to rate each report with respect to abuse/dependence or withdrawal. Reports generated by the ISC were sent to the licensee of tramadol in the USA, OMP, to be submitted via the MedWatch system to the FDA.

II) Post-marketing surveillance studies

- Study on the abuse of tramadol in pain patients, the intended users of tramadol.
- Study on the abuse of tramadol in impaired health care professionals, a population considered most likely to experiment with and abuse tramadol at a very early stage.

Data from the proactive surveillance programme

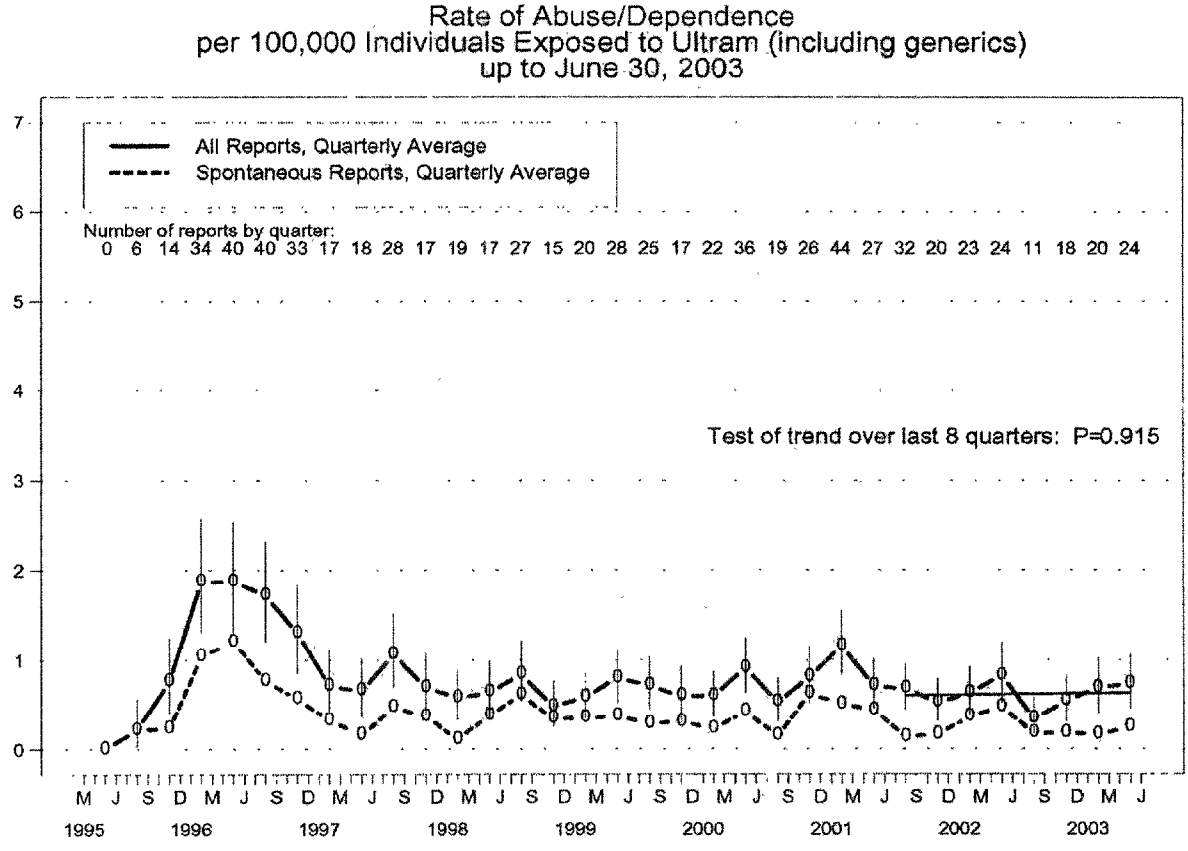
Spontaneous reports and proactively collected reports by the ISC

After the first year of launch, monthly patient exposure to tramadol reached approximately 700,000 new patients per month and close to 400,000 continuing patients per month. The general trends in new, continuing, and total tramadol exposures have been consistent over the first 7 years of availability in the US. The availability of ULTRACET® (tramadol/APAP) in August 2001 and of generic tramadol in June 2002 has decreased the exposure to branded tramadol ULTRAM®.

From April 1995 to June 30, 2002, the Independent Steering Committee collected a total of 1,920 reports (spontaneous reports and actively collected reports). Only 688 of these reports were assessed by the ISC to be positive or possible cases of tramadol abuse/dependence; a further 294 reports were classified as "alleged" for abuse as they did not represent abuse in the strict diagnostic criteria. Six-hundred and one cases referred to withdrawal alone with no indication of abuse.

Reports of abuse of tramadol reached an expected peak in the first three quarters of 1996 of approximately 2-3 cases per month per 100,000 patients as a result of tramadol's US launch in 1995. Subsequently, the rate decreased to an average of approximately 1 case per 100,000 patients (Figure 4).[10]

Figure 4:



The solid line in this figure represents the total rate reported (including reports proactively collected by the ISC through their information network), while the dotted line represents the spontaneous reporting rate.

In over 90% of the cases of tramadol abuse/dependence there was a history of opiate, alcohol or other drug abuse.

Data through December 2003[10] did not show any critical development; the reporting rate for abuse/dependence was still below 1 case per 100,000 patients.

Geographical analysis

Geographical analysis of reports on tramadol abuse/dependence showed that tramadol abuse was confined to isolated pockets in the country and was transient in nature. High levels of abuse were not detected in large, metropolitan areas where heroin and other drug use are prevalent.

Internet discussion of tramadol

The ISC internet searches indicated that within 2 months of tramadol's launch, there was extensive discussion of tramadol in the Internet, primarily by individuals asking whether tramadol had mood-altering effects. While a very small number (< 12) indicated that tramadol could be used to alter mood or enhance effects of other drugs, over 90% of the discussions indicated that tramadol was devoid of any beneficial euphorigenic effect. Recent reviews of internet drug abuse sites indicate little interest in tramadol.

Postmarketing surveillance studies

Abuse potential in pain patients

An open, randomised study in chronic pain patients had three treatment arms: tramadol, NSAID, and hydrocodone. The study aimed to compare the rate of abuse of tramadol with that of NSAIDs, known to be very low, and that with medications containing hydrocodone, a drug known to have a significant risk of abuse.

A total of 11,352 patients were enrolled and surveyed by telephone 9 times over a 12 month period; in total, 87,180 interviews were completed. The final sample was composed of 3,145 subjects initially prescribed hydrocodone, 4,039 subjects initially prescribed NSAIDs, and 4,168 subjects initially prescribed tramadol.

An initial analysis indicated that the majority of subjects (97.4%) were taking tramadol "as prescribed" or "less than prescribed" and well within the recommended daily dose. At the subject level, the rate of abuse associated with tramadol was 0.7%, which was similar to that associated with NSAIDS (0.5%), and significantly less than the rate associated with hydrocodone (1.2%).[11]

Abuse potential in impaired health professionals*

Impaired health care professionals were selected for the second Phase IV study because they are at high risk and have very easy access to drugs. Health care professionals were one of the earliest populations to abuse pentazocine and fentanyl citrate.

The purpose of this study was to monitor tramadol use classified as prescription use, non-prescribed brief use (experimental use), and non-prescribed sustained use (abuse/dependence) among a sample of health care professionals between November 1995 and August 1998.[12]

Data were collected on over 1600 individuals. All participants completed an intake form and were monitored by behavioural measures and urine toxicology for use of drugs including tramadol for 3 years. A small percentage of individuals tested positive for tramadol (1.1%) without any indication that there was a legitimate prescription. Some experimented with tramadol (6.7%), and 0.9% were defined as having a relapse with abuse and dependence. Those who used tramadol were previous opioid abusers and had access to the drug, but did not report liking tramadol.

Conclusion

* Impaired health professionals had previous drug abuse.

The data from the ISC in the USA continue to support low rates of abuse of tramadol. The reporting rate of abuse/dependence was as low as predicted at the beginning of US marketing and decreased over time to an average of around 1 case per 100,000 patients. The ISC further concluded that the risk of abuse was mainly confined to persons with a history of substance abuse, who overall accounted for more than 90% of abuse cases. Since tramadol is not recommended in persons with a history of substance abuse, it can be concluded that if tramadol is prescribed properly, there should be little risk of abuse. Where low levels of abuse occurred, it was transient in nature, reflecting experimentation.

Initial data from phase IV studies on tramadol's abuse risk in low and high risk groups support tramadol's relatively low risk of abuse. In a study in pain patients, abuse of tramadol was significantly less than that for hydrocodone and comparable to the negative control, NSAIDs. A study in impaired health professionals, a high risk group for abuse, showed that some subjects experimented with tramadol but then discontinued.

The Drug Abuse Advisory Committee (DAAC) meeting sponsored by the US FDA in 1998 confirmed their 1994 recommendation to keep tramadol unscheduled on the basis of the ISC data.[13]

6.4 The Drug Abuse Warning Network (DAWN)

Background

The Drug Abuse Warning Network (DAWN) is a US data collection system that was established to monitor the health consequences associated with the use and abuse of drugs. The data are collected by retrospective record review in a representative sample drawn from 4,700 hospitals in the US that have 24-hour emergency rooms. In these retrospective, epidemiological studies, emergency room mentions of a medication are tabulated as an indicator of the consequences of drug use and abuse. The DAWN system was redesigned and implementation of the New DAWN began in 2003.

The Old DAWN definition of abuse is broad and includes:

- The use of prescription drugs in a manner inconsistent with accepted medical practice
- The use of over-the-counter (OTC) drugs contrary to approved labelling

- The use of any other substance (heroin, cocaine, marijuana, glue aerosols, etc.) for psychic effect, dependence, or suicide

Old DAWN was discontinued in 2002 and new sample, questionnaire and case identification procedures were implemented. In addition to changes in chart review procedures such as the reporting form, a key difference is that the New DAWN collects data on all cases involving a particular drug whether it is associated with abuse or not. For example, the New DAWN collects data on adverse reactions, overmedication and accidental ingestion where the Old DAWN collected data on drug abuse-related cases, with the exception of suicide attempts. Thus the Old DAWN and the New DAWN are not comparable in any way.

This review includes data from the Old DAWN for the period 1995 to 2002 and the unweighted aggregate data from New DAWN for 2003 to December 2005. Data from 2002 were examined with regard to motivation, reason for contact, single or multidrug episode etc.

Analysis of Old DAWN

The DAWN data were analyzed for mentions on tramadol and its ranking in the database. For comparison to other drugs, comparative rates of abuse were calculated by taking the number of DAWN reports in relation to the number of prescriptions of the drug in 2000 (IMS).

Results of Old DAWN:

During the year 2000, there were 1,810 mentions of tramadol of which more than half were suicides, not considered as abuse (Table 4). This is a relatively small number of mentions considering that number of hospitals in the DAWN system.

Data from the old DAWN indicate that the number of mentions in DAWN stabilized over the 3-year period between 2001 and 2002. The number of mentions per 100,000 prescriptions was also relatively stable ranging from 15.2 to 18.3 DAWN mentions per 100,000 prescriptions. This rate is much lower than other drugs reported in Old DAWN, both scheduled and not scheduled.

Tramadol rates have remained constant over seven years as shown in Table 4.

Table 4: Trends in Ultram-Related DAWN Cases per 100,000 Prescriptions 1995-2002

Year	1995*	1996	1997	1998	1999	2000	2001	2002
#DAWN Cases	645	1,290	1,418	1,972	1,113	1,810	2,329	1,714
Rate per 100,000 Rx	14.7	13.3	~14.5	18.5	9.9	15.8	18.3	15.2

* Six months of data were collected.

Rates by numbers of prescriptions provide a rough estimate of relative rates. A comparison of rates of DAWN mentions per 100,000 prescriptions is shown in Table 5. Tramadol's rate is lower than several other drugs that have been scheduled as well as unscheduled drugs such as amitriptyline and fluoxetine.

Table 5: DAWN mentions/ 100,000 prescriptions for selected drugs in 2000

Drug	Rates/ 100,000 prescriptions	International Schedule
Hydromorphone	373	1961 Convention
Chlordiazepoxide	351	1971 Convention
Amitriptyline	37	unscheduled
Hydrocodone	26	1961 Convention
Propoxyphene	22	1961 Convention
Fluoxetine	45	unscheduled
Tramadol	16	unscheduled

In 2002, there were 1,714 Old DAWN mentions associated with the use of tramadol. Approximately half (48%) were female and age 35 or older. Fifty percent of the mentions listed suicide attempt or gesture as the motivation and 77% were in combination with alcohol or another drug. Psychic effects were listed as the motivation for the visit in only 11% of the ED visits (Table 6).

Suicide as a motivation is often associated with DAWN reports of drugs that are usually not associated with drug abuse. For example, suicide is listed as the motivation in half (50%) of the DAWN mentions of

phenytoin, and 75% of NSAID mentions. In contrast, for drugs such as oxycodone and hydrocodone, suicide is listed as the motivation in 18% and 35% of mentions, respectively.

Table 6: Distribution of Old DAWN Mentions of Tramadol by Selected Variables for 2002
N =1,714

	n	%
Gender		
Male	833	48.6
Female	815	47.5
Age		
12-17	...	
18-25	286	16.7
26-34	225	13.1
35-44	593	34.6
45-54	233	13.6
55+	...	
Motivation		
Psychic Effects	181	10.6
Dependence	461	26.9
Suicide	855	49.9
Other/Unknown	...	
Drugs Involved		
Only Tramadol	405	23.6
Plus alcohol	...	
Other drugs no alcohol	810	47.3
Other drugs plus alcohol	293	17.1

Analysis of New DAWN

The new DAWN system classifies cases based upon a decision tree in which the type of case is assigned hierarchically. The hierarchy is as follows:

1. Suicide attempt
2. Seeking Detox
3. Alcohol only (age < 21)
4. Adverse Reaction
5. Overmedication

6. Malicious poisoning
7. Accidental Ingestion
8. Other

Key definitions for the purposes of this paper are "Overmedication" and "Other." The definitions below are taken directly from the DAWN ED Reference Guide.

Overmedication – These patients took more than the recommended dose of a prescription or OTC drug or dietary supplement. This includes, but is not limited to, the following reasons:

- Patients who forgot they had already taken a dose
- Those who took extra dose(s) to make up for a missed dose
- Patients who took more medication because their symptoms did not subside with the recommended dose

This case type includes patients who took more than the recommended dose for recreational or abuse purposes. Illicit drugs are not included in this case type.

Other – This includes all other drugs and substances not classified above. This category includes all other cases in which drug dependence, abuse, withdrawal, suicidal ideation or gesture, recreational use, or reason unknown (patient comatose) caused or contributed to the ED visit.

Data from the New DAWN for Tramadol was examined for the period January 1, 2003 to December 28, 2005. Also, New DAWN data is available "live" and this is close to real time data, the numbers vary according to the time in which the data are run so that more than one time frame may be included in this report.

Results of New DAWN

An examination of the unweighted tramadol reports in New DAWN for the period January 2003 to December 28, 2005 indicates a total of 2,174 reports for the period. Sixty-four percent of the cases were

female and age 35 or older. Adverse Reaction (44.2%), Overmedication (24.5%), Other (13.5%), and Suicide (10.1%) were the most prevalent types of cases. Overdose (33.8%), Other (33.7%), Digestive Problems (22.2%), Altered Mental Status (17.1%), and Psychiatric Condition (13.4%) account for the majority of the complaints (Table 7).

Table 7: Distribution of Combined Unweighted Tramadol New DAWN Cases by Selected Variables for the Period 2003 – December 28, 2005
N = 2,174

	n	%
Gender		
Male	775	35.6
Female	1,397	64.3
Age		
0-20	195	8.9
21-34	593	27.3
35-44	495	22.8
45-54	382	17.6
55+	509	23.4
Type of Case		
Suicide Attempt	219	10.1
Seeking Detox	122	5.6
Adverse Reaction	961	44.2
Overmedication	532	24.5
Malicious Poisoning	0	0
Accidental Ingestion	47	2.2
Other	293	13.5
Chief Complaint		
Overdose	734	33.8
Intoxication	95	4.4
Seizures	144	6.6
Altered Mental Status	372	17.1
Psychiatric Condition	292	13.4
Withdrawal	127	5.8
Seek/Detox	124	5.8
Accident/injury/assault	59	2.7
Abscess/cellulitis/skin/tissue	209	4.8
Chest Pain	95	4.4
Respiratory problems	139	6.4
Digestive Problems	483	22.2
Other	732	33.7
Total Complaints	3,605	
Complaints/Case	1.7	

"Other" is the category that is the primary indicator of drug abuse. For tramadol, "Other" accounts for 13.5% of cases compared to 13.7% for Acetaminophen-Diphenhydramine, 12.1% for all Acetaminophen

non-narcotic combinations, 7.8% for APAP and tramadol and 23.2% for hydrocodone combinations (Table 8). The rates for "Other" for tramadol versus the acetaminophen combination products were not significantly different, but all were significantly less than hydrocodone combinations.

The Substance Abuse and Mental Health Administration (SAMHSA) states that overmedication represents misuse of prescription or over-the-counter medications. It is clearly misuse when the drug is used for recreational or abuse purposes. However the proportion of abuse cases in relation to all overmedication cases is unknown. For reporting purposes, the SAMHSA combines "Overmedication, Malicious Poisoning and Other" and refers to the combined total as "misuse/abuse."

Table 8: Comparison of Selected Characteristics between Tramadol Cases Classified as "Overmedication" or "Other" in New DAWN January 1, 2003-December 28, 2005

	Overmedication		Other	
	N	%	n	%
Gender	532		293	
Male	200	37.6	132	45.1
Female	332	62.4	161	54.9
Age				
0-20	43	8.2	35	11.9
21-34	150	28.2	95	32.4
35-44	137	25.6	77	26.3
45-54	114	21.4	55	18.8
55+	88	16.5	31	10.6
Chief Complaint				
Overdose	395	74.2	105	35.8
Intoxication	34	6.4	35	11.9
Seizures	48	9.0	24	8.2
Altered Mental Status	137	25.6	60	20.5
Psychiatric Condition	95	17.9	49	16.7
Withdrawal	6	<1	76	25.9
Seek/Detox	2	<1	2	<1
Accident/ injury/assault	15	2.8	13	4.4
Abscess/cellulitis/skin/tissue	4	<1	9	3.1
Chest Pain	20	3.8	11	3.8
Respiratory problems	20	3.8	15	5.1
Digestive Problems	42	7.9	40	13.7
Other	98	18.4	84	28.7
Total Complaints	916		523	
Complaints/Case	1.7		1.8	

A review of Tables 8 and 9 suggests that the populations classified as "Overmedication" and "Other" are different in terms of gender, age, and chief complaint so it may be misleading to combine them. Rather, the two types of cases should be considered separately. This also serves to reduce the risk that the combined number is quoted as the estimate of abuse or addiction.

Table 9: Comparison of Selected Characteristics between Cases Classified as Overmedication or Other for Codeine/Combinations and Oxycodone/Combinations for the Period 2003-2004

	Codeine Combinations				Oxycodone Combinations			
	Overmedication		Other		Overmedication		Other	
N	877		585		2,481		4,223	
Gender	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Male	278	51	298	51	1,139	46**	2,515	60
Female	285	49	285	49	1,338	54	1,706	40
Age								
0-20	163	19	100	17	160	6**	460	11
21-34	278	32	169	29	618	25**	1,509	36
35-44	178	20**	157	27	617	25**	1,166	28
45-54	150	17	107	18	590	24**	752	18
55+	104	12	50	9	490	20**	334	8
Chief Complaint								
Overdose	714	81**	229	37	1,857	75**	946	22
Intoxication	45	5**	58	10	153	6**	330	8
Seizures	6	<1	10	2	22	1	83	2
Altered Mental Status	223	25	123	21	764	31**	704	17
Psychiatric Condition	152	17**	119	20	285	11**	826	20
Withdrawal	4	<1**	44	8	36	1**	1,423	34
Seek/Detox	3	<1**	7	1	7	<1	117	3
Accident/ injury/assault	14	2**	30	5	60	2**	154	4
Abscess/cellulitis/skin/tissue	9	1*	17	3	27	1**	112	3
Chest Pain	15	2*	21	4	36	1**	176	4
Respiratory problems	15	2*	24	4	100	4**	186	4
Digestive Problems	62	7*	63	11	99	4**	558	13
Other	143	16	156	27	408	16**	1,056	25
Total Complaints	1405		901		3,854		6,671	
Complaints/Case	1.6		1.5		1.5		1.6	

Conclusion

Data from the old DAWN suggest that the tramadol cases were most likely associated with suicide attempts involving multiple drugs and not drug abuse in the sense of recreational drug use or addiction. Furthermore the rate of DAWN cases per 100,000 prescriptions was relatively low compared to other drugs both scheduled and not scheduled and the rate has been stable over time.

Data from New DAWN paint a similar picture. The New DAWN collects 8 different cases type with "Other" representing drug abuse. Over the period from January 2003 to December 28, 2005, a total of 2,174 cases associated with tramadol were reported. Of these, 13.5% were classified as "Other." This figure is similar to that for acetaminophen combinations and markedly less than for hydrocodone combinations. During the same time frame a total of 612 cases of acetaminophen and tramadol were reported and only 7.8% were classified as "Other."

These data from the Old DAWN and New DAWN systems are consistent in that they clearly demonstrate that tramadol is neither a drug abuse problem nor a significant public health risk.

6.5 The Substance Abuse Warning System (SAWS)

Background

From 1976-2000, post-marketing abuse patterns of chemical substances in the Federal Republic of Germany were monitored through a substance abuse monitoring system (SAWS) devised by Professor Wolfram Keup in 1975, sometimes denoted as "early warning system" (EWS). Each year, a random sample of 700-900 in-patient addicts were interviewed regarding substance abuse history in a variety of treatment facilities. Roughly one-third were alcohol abusers, one-third were medicinal drug abusers and one-third were drug addicts.

The objective of the system is to detect changes in abuse patterns of chemical substances.

Results

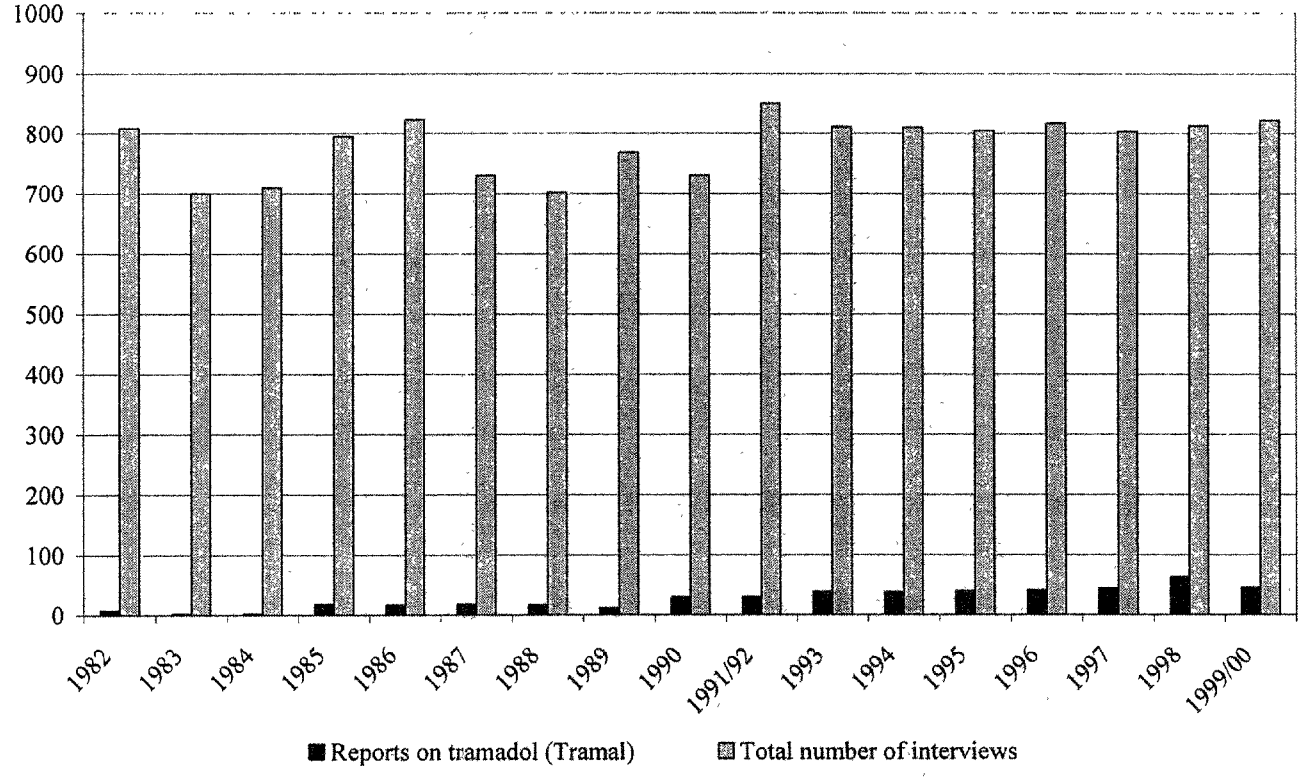
In the random sample of the SAWS system, 14,702 patients with abuse problems were assessed over a period of 25 years (between 1976 and 2000). Six–thousand two-hundred and twenty-two were alcoholics, 2,921 medicinal drug abusers and 5,540 drug addicts.

Among the random sample of 14,702 patients, 460 abuse cases of tramadol (Tramal®) were identified. The majority of the reports (454) were related to immediate-release formulations of tramadol and six to the sustained-release formulation of tramadol (launched in 1994).

Time profile

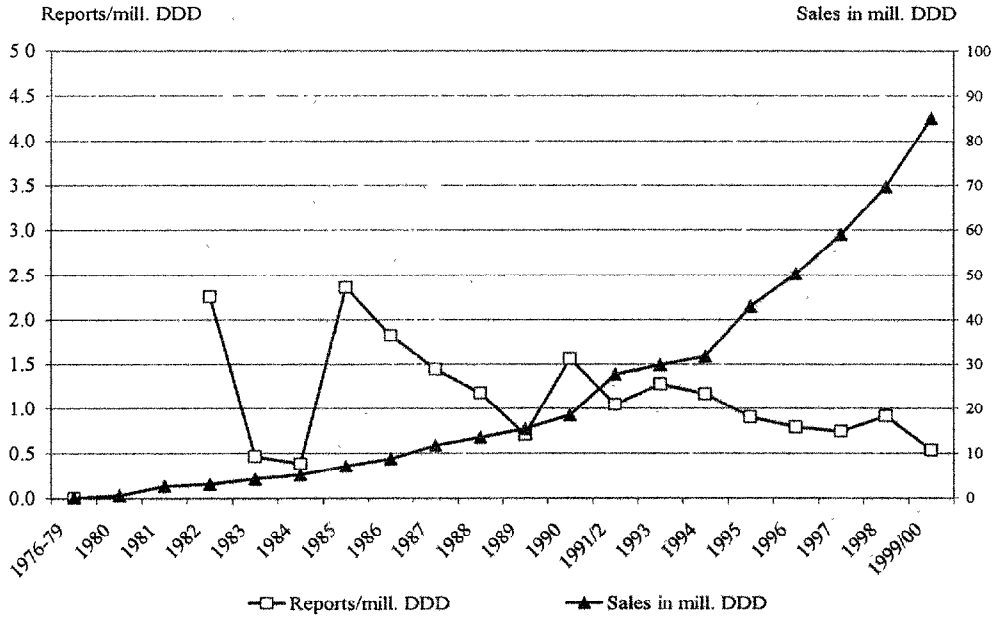
Figure 5 shows the number of reports on tramadol and the total cases per year in the SAWS system. Tramadol abuse cases are only a small part of the total reports per year in this system. The number of reports on tramadol has increased slowly since 1990. The last bar (and the 1991/92 bar) represents 2 years worth of data.

Figure 5. Comparison of total cases to tramadol mentions (Tramal®), 1982-2000



In parallel to the slow increase of reports in the SAWS system between 1990 and 2000, tramadol exposure increased substantially in this period. As shown in Figure 6, the number of SAWS reports on tramadol in relation to tramadol exposure decreased over time.

Figure 6: Tramadol sales in defined daily doses (DDD = 300 mg) and tramadol reports/1 mill. DDD;
(SAWS data 1976-2000, Grünenthal sales statistics before 1993, IMS Kilochem statistics for 1993-2000)



Abuse patterns

Ninety-five percent of the tramadol cases involves the use of multiple drugs. Tramadol rarely is the source for medicinal abuse careers; nine such cases are in the SAWS database.

Most significantly, there was no case where use of tramadol led to a history of drug addiction.

Drug addicts tried tramadol as a drug for withdrawal treatment or as a substitute for heroin. The opioid effect of tramadol was generally not sufficient. Tramadol appears to arouse curiosity and experimentation,

but experimentation apparently provides little incentive for continued use. These data are consistent with data from the ISC in the US.

Conclusion of SAWS Data

Relative to increasing patient exposure, tramadol abuse reporting rates in the SAWS system decreased over time. On the basis of the data, Professor Keup concluded that in Germany, "a stricter control of tramadol is not desirable at present."[14]

6.6 Forensic and toxic exposure information systems

National Forensic Laboratory Information System (NFLIS)

The NFLIS is a computerized database of analyzed drug exhibits from state and local forensic laboratories that was developed by the Research Triangle Institute under contract to the US Drug Enforcement Administration in 1997. The system began reporting data in 1998. By September 30, 2001, 145 of the estimated 276 state and local labs that perform solid dosage drug analysis had been recruited into NFLIS. As of March 2005, the system has grown to include 41 state systems and 81 local or municipal laboratory systems representing 244 individual labs. These labs analyze nearly 71% of the nation's estimated 1.2 million annual state and local drug cases. Data from the System to Retrieve Information from Drug Evidence (STRIDE) is now included in the NFLIS database.

Initially, the NFLIS did not support trend analysis because the system was still in an implementation phase. However, the system collected enough information to provide national estimates beginning in 2001. For example, in 2000, the estimated number of law enforcement drug seizures was 499,760 while the national case estimates for the period 2001-2003 were approximately 1.3 million.

National estimates are generated for drug items and drug cases based on a statistical sample of 165 laboratories including 29 state laboratory systems and 31 local labs that report data for 6 or more months. Section 2 of the NFLIS report consists of unweighted numbers of law enforcement drug seizures from all

labs that reported data for 6 or more months. For this section of the NFLIS report, it appears that the system stabilized in 2002 rather than 2001.

NFLIS results are made available through quarterly and annual reports. These reports provide statistically representative national and regional estimates for the most frequently identified drugs. National case estimates for the most commonly identified drugs are also presented in the reports. These reports also include findings on major drug categories such as narcotic analgesics, benzodiazepines, club drugs, anabolic steroids, and stimulants (Section 2 of the NFLIS report). Unlike the national estimates which are based on a national sample of laboratories, Section 2 includes data submitted by all participating labs that reported 6 or more months during the year. Also included in Section 2 of the report are data on drug combinations, drug purity for heroin and cocaine, and some city data for the top 4 drugs.

Over the next several years, the DEA will seek to expand the NFLIS project to include all state, local, and federal laboratories that perform solid dosage drug analyses. As an initial step, the domestic data from STRIDE II have been added to the NFLIS database, as noted above. The wider scope of NFLIS compared to STRIDE is exemplified by the fact that STRIDE reported 51,830 drug items while the NFLIS National and Regional estimates were based on 1.7 million analyzed items in 2004.

A major strength of the NFLIS is its size, which renders it somewhat less susceptible to variations in police activity than STRIDE, although caution is still advisable.

Differences in regional trends may reflect different drug enforcement priorities and laboratory policies that can influence the types of drugs submitted to be analyzed by laboratories. A potential example of the impact of lab policies is found in the 2002 Annual Report section on drug combinations. Of the 11,519 drug items containing two or more substances that were reported, 1,037 (9%) contained hydrocodone and acetaminophen. Based on the unweighted data from all reporting labs, this should have been closer to 9,500. It is likely that once hydrocodone was found in the lab, they didn't proceed with further analysis.

Method of Analysis for NFLIS Data

The analysis focuses on the data from 2000 to 2004 for pharmaceutical opioids and tramadol obtained from published reports. Although data for the year 2000 are published, the system was still in the implementation phase and data are not useful for trends. Data are presented as a percentage of total analgesics. While trends can be analyzed for the period 2002-2004, changes in the proportion of drug mentions over time can be assessed for the previous years.

Results of NFLIS Data

In general, analgesics represent a fraction of all seizures. Cannabis, cocaine, methamphetamine, and heroin account for more than 84% of all seizures. The remainder of the top 25, including hydrocodone, oxycodone, methadone, codeine, morphine and propoxyphene account for an additional 8.6% of total seizures. Acetaminophen (5,300) is 14th on the list of the top 25.

Tramadol represents 0.026% of total seizures and less than 1% of narcotic seizures. The proportion of tramadol seizures compared to all analgesic seizures has remained relatively constant at these low levels over time (Table 10). Given the widespread availability of tramadol (more than 13 million prescriptions per year), the small number of seizures reinforces the relative low abuse of tramadol. In contrast, hydromorphone has 2000% fewer prescriptions than tramadol but has approximately twice as many seizures. Hydrocodone is seized 43 times more often than tramadol but is prescribed only 7.5 times more than tramadol.

These data are consistent with an independent study of drug diversion investigators which show that seizures of tramadol are at the bottom of the list.[15]

Table 10: Distribution of Selected Drug Seizures from the Top NFLIS 2000 – 2004[1,2]

	2000		2001		2002		2003		2004	
	N	%[3]	N	%	N	%	N	%	N	%
Hydrocodone	3,014	39.2	5,890	36.9	9,563	34.4	10,195	36.2	13,113	35.5
Oxycodone	2,116	27.6	5,181	32.5	8,660	31.2	8,576	30.4	11,342	30.7
Codeine	926	12.1	1,537	9.6	1,911	6.9	1,824	6.5	2,454	6.6
Propoxyphene	570	7.4	1,022	6.4	1,526	5.5	1,321	4.7	1,348	3.6
Morphine	459	6.0	872	5.5	1,499	5.4	1,488	5.3	1,902	5.2
Hydromorphone	204	2.7	376	2.4	622	2.2	471	1.7	616	1.7
Meperidine	160	2.1	267	1.7	281	1.0	240	0.9	231	0.6
Nalbuphine	91	1.2	132	0.8	261	0.9	10	0.04	6	0.02
Tramadol	73	1.0	129	0.8	238	0.9	245	0.9	303	0.8
Pentazocine	25	0.3	60	0.4	68	0.2	47	0.2	63	0.2
Fentanyl	23	0.3	33	0.2	86	0.3	152	0.5	198	0.5
Buprenorphine	8	0.1	11	0.07	11	0.04	9	0.03	148	0.4
Butorphanol	5	0.07	5	0.03	8	0.03	8	0.03	5	0.01
Methadone					2,327[5]	8.4	2,781	9.9	3,904	10.6
Other	6	0.08	450	2.8	722	2.6	809	2.9	1,318	3.6
Total Analgesics	7,680	1.4[4]	15,965	1.9	27,783	2.7	28,176	2.7	36,951	3.2
Total Seizures	532,412		848,713		1,034,032		1,042,167		1,160,017	

[1] Data are actual data reported by labs at least 6 months of data and are not national estimates from the national sample.
[2] Data cannot be used for trend analysis prior to 2002.
[3] Percent based on total analgesics.
[4] Percent analgesics of total seizures
[5] Methadone included with Narcotic Analgesics

Conclusion for NFLIS Data

These numbers reflect the low levels of abuse of tramadol and are consistent with other US data such as those obtained from the Drug Abuse Warning Network (DAWN) and the Key Informant Network of the ISC.

The Toxic Exposure Surveillance System (TESS)

The Toxic Exposure Surveillance System (TESS) was established in 1983 by the American Association of Poison Control Centers (AAPCC) as the only comprehensive poisoning surveillance database in the United States. The TESS data are collected by 63 participating centers and reported to the AAPCC, including fatalities.[16] For example in 2000, 59 out of 63 centers reported data for the entire year and in 2004, 60 out of 62 centers did so. A total population of 270.6 million was served by the participating centres in 2000. These data represent an estimated 96.2% of the human poison exposures that precipitated poison centre contacts in the US during 2000.

The data are used for post marketing surveillance to identify and detect chemical and bioterrorism incidents as well as exposures to intentional poisoning and unintentional poisoning to pharmaceuticals. Data on the severity of exposure are also collected. The definitions for chronicity, reason for exposure, and medical outcome can be found in Appendix 3.

Reasons for exposures were coded according to unintentional and intentional poisoning (including suicide, abuse, misuse), adverse reactions and other. The TESS database contains a cumulative total of 38,655,222 human exposures. In 2004, a total of 2,438,644 exposures was reported. In addition to exposure calls, more than 1 million information calls were also received. Drug identification calls accounted for more than half (~56%) of the information calls and another 14% related to drug information such as drug interactions, indications, and adverse events.

Of the 2,438,644 exposures in 2004, a total of 301,254 (12.4%) were classified as intentional. Of those intentional exposures, the majority, 196,164 (65%), were suspected suicide; 45,562 (15%) were classified as abuse; 43,514 (14%) as misuse; and 16,014 (5%) were unknown. Analgesics were involved in 279,955 (11.5%) of the human exposures. A total of 113,841 (41%) of analgesic exposures was intentional.

Methods of Analyzing TESS

Data from the Toxic Exposure Surveillance System were obtained from the Annual Reports of the American Association of Poison Control Centers (AAPCC). Trend data were examined for the period from 2001 to 2004 for intentional exposures to analgesics containing hydrocodone, oxycodone, propoxyphene, codeine, and tramadol. With the exception of tramadol, these products are primarily formulated in combination with acetaminophen or aspirin. Tramadol is also available in combination with acetaminophen. Methadone and morphine are single-entity products. Additional analyses were performed on detailed data obtained from the AAPCC for 2004. The sub-analyses were conducted to separate suicide attempts or gestures from abuse cases and to look at issues of chronicity and multiple drug use.

Results of TESS Analysis

The intentional exposures associated with hydrocodone and oxycodone-containing analgesics have been increasing over the last few years, while those associated with propoxyphene and codeine have remained relatively stable. In contrast, trends in intentional exposures for single-entity products such as morphine and methadone have more than doubled since 2001, perhaps reflecting their increased use in the treatment of pain (Table 11). There was an increase in intentional exposures associated with tramadol between 2001 and 2004. This increase is entirely associated with the introduction of tramadol with acetaminophen; the trend for the single-entity product was flat.

Table 11: Distribution of Intentional Exposures in TESS for Selected Opioid Analgesics 2001 – 2004

	2001	2002	2003	2004
All Hydrocodone	8,804	10,282	11,296	13,341
All Oxycodone	4,974	5,450	5,874	6,816
All Propoxyphene	3,837	3,885	3,757	3,769
All Codeine	3,649	3,545	3,245	3,272
All Tramadol	2,109	1,712[1]	2,362[1]	2,823[1]
Methadone[2]	1,109	1,697	1,881	2,437
Morphine[2]	878	1,064	1,213	1,483

[2] 2002-2004 includes tramadol/APAP
[2] Single-entity opioids

It is important to recognize that intentional exposures do not necessarily reflect abuse. They may also reflect suicide attempts or gestures as well as misuse of the product. In order to better understand the reasons behind intentional exposure, additional analysis of the tramadol and tramadol/APAP intentional exposures for 2004 was undertaken.

A review of the TESS data for 2004 indicates that there was a total of 2,159 intentional exposures of tramadol and 752 intentional exposures associated with tramadol with acetaminophen. A breakdown of the cases by reason for exposure is listed below (Table 12).

Note the difference in the distribution of tramadol-containing analgesics to all TESS cases (11.1% and 8.4% abuse versus 15%; 70.6% and 73.1% suspected suicide versus 65%).

Table 12
Distribution of Intentional Tramadol Exposures in TESS by Reason for Exposure 2004

	Tramadol		Tramadol/APAP	
REASON	**N**	**%**	**N**	**%**
Abuse	240	11.1	63	8.4
Misuse	272	12.6	89	11.8
Suspected Suicide	1,524	70.6	550	73.1

Unknown	123	5.7	50	6.6
Total	**2,159**	**100.0**	**752**	**99.9**

Of the 2,911 cases associated with tramadol or tramadol with acetaminophen more than 70% are associated with suicide attempts or gestures, and approximately 10% are reported as abuse. In almost 70% of the abuse cases, the medical outcome was classified as "unrelated, no effect, minimal effect possible, or minor effect." (Table 13)

Table 13: Distribution of Medical Outcome by Reason for Exposure for Single Entity Tramadol 2004

Reason	Abuse		Misuse		Suspected Suicide		Unknown	
Medical Outcome	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Minor Effect	65	27.1	49	18.0	362	23.8	37	30.1
Moderate Effect	30	12.5	46	16.9	264	17.3	12	9.8
Major Effect	10	4.2	10	3.7	70		4	3.3
No Effect	58	24.2	62	22.8	321	4.6	13	10.6
Not followed nontoxic or minimal clinical effects possible	40	16.7	55	20.2	276	18.1	40	32.5
Unable to follow Potentially Toxic Effects	32	13.3	40	14.7	191	12.5	9	7.3
Unrelated	5	2.1	8	2.9	35	2.3	7	5.7
Death	0	0	1	<1	4	<1	1	<1
Total	240		272		1,524		123	

Further review of the 303 "abuse" cases for tramadol and tramadol/APAP indicates that slightly more than half (52%) involved multiple drugs and that almost 90% involved acute exposure. In only 11 of the "abuse" cases was the exposure classified as chronic (Table 14). In 17 cases, the exposure was classified as acute or chronic. While there is some variation in these numbers between the single-entity and the combination product, the pattern is consistent across both formulations.

Table 14: Distribution of Medical Outcome, Chronicity, and Number of Drugs Involved with Tramadol and Tramadol/APAP Abuse Cases 2004

	Tramadol		Tramadol/APAP		Total	
N	240		63		303	
Medical Outcome	**n**	**%**	**n**	**%**	**N**	**%**
Minor Effect	65	**27.1**	10	**15.9**	75	**24.8**
Moderate Effect	30	**12.5**	8	**12.7**	38	**12.5**
Major Effect	10	**4.2**	0	**0**	10	**3.3**
No Effect	58	**24.2**	24	**38.1**	82	**27.1**
Not followed nontoxic or minimal clinical effects possible	40	**16.7**	5	**7.9**	45	**14.9**
Unable to follow Potentially Toxic Effects	32	**13.3**	14	**22.2**	46	**15.2**
Unrelated	5	**2.1**	1	**1.6**	6	**2.0**
Death	0	**0**	1	**1.6**	1	**0.3**
Chronicity						
Acute	216	**90.0**	50	**79.4**	266	**87.8**
Acute or Chronic	9	**3.8**	8	**12.7**	17	**5.6**
Chronic	10	**4.2**	1	**1.6**	11	**3.6**
Unknown	5	**2.1**	4	**6.3**	9	**3.0**
# Drugs						
1	115	**47.9**	29	**46.0**	144	**47.5**
2	66	**27.5**	15	**23.8**	81	**26.7**
≥3	59	**24.6**	19	**30.2**	78	**25.7**

In summary, among all intentional exposures associated with tramadol-containing analgesics, the actual rate of abuse was low, medical outcomes were generally minor, and the exposure was acute not chronic, suggesting experimentation rather than compulsive use. This is consistent with other data of tramadol abuse.

Conclusion

Data from US forensic laboratories (NFLIS) and poison control centers (TESS) in the USA suggest little abuse and no significant public health risk associated with tramadol.

6.7 National Household Survey on Drug Use and Health (NHSDUH)

The National Household Survey on Drug Use and Health has been conducted since 1972. Since the early 1990's it has been operated under contract by the Substance Abuse and Mental Health Services Administration (SAMHSA). Data are collected from more than 70,000 household respondents about their use of illicit drugs and the use of licit drugs for non-medical purposes. In the 2004 report, more than 110 million people reported their nonmedical lifetime use of illicit drugs. More than 31 million reported the lifetime use of pain relievers and approximately 4.4 million reported use of pain relievers in the past month. It is important to note that lifetime use means that the respondent reports using a drug for non medical purposes at least once in their life.

The question is phrased as follows: Have you ever used _____that was not prescribed for you or that you took only for the experience or feeling it caused?

The 2004 NHSDUH data suggest that of the 31,768,000 that have used a pain reliever nonmedically, 8.8 million have tried propoxyphene or codeine, 7.4 million have tried hydrocodone, 5 million have tried oxycodone and 0.5 million have tried tramadol at least once. These data suggest that there is little interest in the nonmedical use or abuse of tramadol.

6.8 Scientific literature: case reports and patient series

As the worldwide exposure to tramadol increases to a total of 823 million defined daily doses (DDD = 300 mg), a handful of individual case reports has emerged reporting either physical withdrawal or abuse. In the latest worldwide literature search of December 22, 2005, there are five case reports in addition to the last analysis for the critical in 2002, 2 of which involve abuse and 3 involving withdrawal. The three cases of withdrawal show that the "severity of withdrawal may be a function of the patient's prior opioid exposure."[17-19] All three cases highlight the need to gradually decrease the dose in the long-term use of tramadol. As noted above, physical withdrawal is an expected outcome of long-term use of a variety of medications including anti-hypertensives, barbiturates, benzodiazepines, opioids and steroids.

In the two cases of abuse, both patients had gradually increased their dose of tramadol to 30 50-mg tablets daily.[20,21] Their subsequent dependence led to withdrawal syndrome that was treated by tapering doses of methadone for the patient who had previous pentacozine and alcohol dependence[20] and tramadol with celecoxib, metoprolol, and hydroxyzine for the patient with no previous dependence history.[21]

While sporadic individual case studies of withdrawal continue to appear in literature searches, it should be noted that the number of studies on the therapeutic benefits of tramadol are greater.[22-24]

Appendix 4 gives an overview of 21 publications on case reports or patient series of tramadol abuse/dependence or withdrawal syndrome collected until December 22, 2005.

US: Nine publications describe case reports on dependence/abuse or withdrawal (6 publications), summarise spontaneous reports received by the FDA until 1996 (1 publication), refer to tramadol abuse in the Cincinnati area of the USA, and report from pharmacists on tramadol abuse (1 publication each). The extent and nature of tramadol abuse in the USA have been extensively investigated by a structured post-marketing surveillance programme on tramadol (ISC).

Germany: Three publications refer to single case reports on withdrawal or dependence. One publication describes tramadol cases investigated by the Institute of Forensic Medicine in Munich. It refers to test results from blood samples for 74 cases collected between 1995 and the middle of 1999, involving 22 cases of death and 52 samples taken from people charged with motoring and criminal offences. Tramadol abuse in Germany has been monitored by the SAWS system and data are also available from the spontaneous reporting system to further evaluate the abuse risk of tramadol (see above).

The rest of the publications came from Italy, Spain, France, Denmark, UK and the Czech Republic. Cases of withdrawal and abuse were reported. Withdrawal is an expected component of continued exposure of many medications such as steroids, benzodiazepines, and opioids. By itself, withdrawal does not reflect abuse or dependence as defined by the accepted medical literature.

7. Control Status

7.1 Current Status

Tramadol is available in more than 100 countries and registered as a prescription-only drug. The compound has been available in some of these markets for a considerable time.

Tramadol is not subject to international control under either the 1961 or the 1971 Conventions.[1]

In 29* of the 104 countries, tramadol is subject to further controls. In 26 of these 29 countries, tramadol is included in a psychotropic-like schedule; tramadol has a narcotic status in only three countries (with a codeine-like status in 2 countries). Appendix 5 gives an overview of tramadol's current national control status world-wide.

Tramadol is an unscheduled medication in the majority of countries in which it is available.

7.2 Effects of Scheduling

Pain is undertreated, particularly in developing countries. One of the main reasons is the insufficient availability of scheduled opioids such as morphine due to strict regulations and opiophobia that occurs

* 12 countries refer to the former USSR, now the Commonwealth of Independent States.

with scheduled opioids. Unfortunately, according to a 1995 survey by the INCB, controlled opioids (narcotics) were insufficiently available for medical purposes. The INCB and WHO have noted the tendency that "legislators sometimes enact laws that not only deal with the illicit traffic itself, but also impinge on some aspects of licit trade and use." An INCB survey of 209 governments asked which factors would impede the medical use of opioids. Of the 65 countries (31%) that responded, 59% cited laws and/or regulations that restricted opioid use, 38% stated that fear of loss or theft was a factor, and 38% stated the administrative burden of regulatory requirements impeded the medical use of opioids in their country.[2] In these countries, the unscheduled centrally-acting analgesic tramadol is used as a stronger alternative to NSAIDS and an alternative to lower dose morphine.

Most of the identified impediments in the 1995 INCB survey were related to concerns about addiction, diversion, restrictive drug laws, insufficient importation of opioids, and inadequacies in healthcare systems. Doctors are poorly educated regarding the use of opioids, potentially leading to "opiophobia." Efforts have been and still are being undertaken to improve this situation, but the problem is not yet solved. In 2000, the International Narcotics Control Board and the WHO drew further attention to this issue in the document "Achieving balance: national opioids control policy":[3]

"...opioids are not sufficiently available for medical purposes. There are a number of reasons, including the low priority for pain management in health care systems, greatly exaggerated fears of addiction, overly restrictive national drug control policies, and problems in procurement, manufacture, and distribution of opioids."

It has been shown that scheduling can also interfere with the availability and use of a drug in developed countries as observed in the USA. In two US surveys of more than 800 physicians, more than half (55%) reported that they would be less likely to prescribe a scheduled medication for chronic pain.[4] This was confirmed by the 30% decrease in butorphanol prescriptions subsequent to scheduling. There were similar decreases in the prescribing of pentazocine in Germany after its scheduling in 1984. This has been shown especially in developing countries, e.g. in India where the consumption of morphine decreased from 715 kg in 1985 to 18 kg in 1997 (INCB 1989/1999) after the Narcotic Drugs & Psychotropic Substances (NDPS) Act passed in 1985.

The implication of these data is clear. Despite the increasing recognition of the undertreatment of pain, unnecessary scheduling may result in a reduction of appropriate prescribing and, in fact, contribute to the problem of unrelieved pain.

Conclusion

Tramadol has become a standard analgesic for the treatment of moderate to moderately-severe or severe pain; it is a stronger alternative to NSAIDS and an alternative to lower-dose morphine. Scheduling of tramadol would restrict its therapeutic use and worsen the existing undertreatment of pain, especially in developing countries.

* * * * * *

Ortho-McNeil, Inc. objects to further consideration by the 34th ECDD without the appropriate pre-review and critical review. The information provided in this response demonstrate that there are no new data indicating any increased risk of diversion from tramadol that would justify a decision to schedule the drug at this time. However, it is clear from even a cursory update of the data that tramadol lacks an abuse potential to warrant scheduling under the international conventions. Its continued availability as a non-controlled analgesic is a considerable benefit to millions of patients who would otherwise not receive appropriate pain treatment.

REFERENCES BY SECTION

SECTION 1: INTRODUCTION

1. Gureje O, Von Korff M, Simon G, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. JAMA 1998; 280:147-51.
2. World Health Organization. *WHO Expert Committee on Drug Dependence. Twenty-eighth report.* (Technical Report Series 836). Geneva, Switzerland: WHO, 1993.
3. World Health Organization. *WHO Drug Information 2000*; Vol. 14, No. 4: 224.
4. World Health Organization. *WHO Expert Committee on Drug Dependence. Thirty-third Report.* WHO, 2003.

SECTION 2: PHARMACOLOGY OF TRAMADOL

1. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. 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.
2. Raffa RB. A novel approach to the pharmacology of analgesics. *Am J Med.* 1996;101(suppl 1A):40S-46S.
3. Frink M, Hennies HH, Englberger W, Haurand M, Wilffert B. Influence of tramadol on neurotransmitter systems of the rat *Arzneim.-Forsch./Drug Res.* 1978;46:1029-1036.
4. Raffa RB, Friderichs E, Reimann W, et al. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. *J Pharmacol Exp Ther.* 1993;267:331-340.
5. Raffa RB, Nayak RK, Liao S, Minn FL. The mechanism(s) of action and pharmacokinetics of tramadol hydrochloride. *Rev Contemp Pharmacol.* 1995;6:485-497.
6. Raffa RB, Friderichs E. The basic science aspect of tramadol hydrochloride. *Pain Rev.* 1996;3:271.
7. Collart L, Luthy C, Dayer P. Partial inhibition of tramadol antiociceptive effect by naloxone in man. *Br J Clin Pharmacol.* 1993;35:73P.
8. 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.
9. Poulsen L, Arendt-Nielsen L, Brozen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther.* 1996;60:636-644.
10. Desmeules J, Violand C, Piguet V, Kondo M, Dayer P. Role of CYP2D6 in tramadol isomers kinetics and analgesic effects [abstract]. *Clin Pharmacol Ther.* 2000;67:91.

SECTION 3: AVAILABILITY AND SALES

1. IMS Kilochem statistics.

SECTION 4: CLINICAL UTILITY

1. Anderson A et al. Treatment of moderate to severe pain: Multicentric observation of administration of the analgesic Tramal®. [Behandlung mäßig starker bis starker Schmerzen: Multizentrische Anwendungsbeobachtung des Analgetikums Tramal®]. *Kassenarzt* 1994; 34(40):44-54
2. Anderson A et al. Pain treatment with prolonged-release tramadol. Results of a post-marketing surveillance study amongst practitioners [Schmerzbehandlung mit Tramadol retard. Ergebnisse einer Anwendungs-beobachtung bei niedergelassenen Ärzten]. Der Kassenarzt 1997;36:38-46.
3. Nossol et al. Treatment of pain with sustained-release tramadol 100, 150, 200 mg: Results of a post-marketing surveillance study. *Int J Clin Pract.* 1998; 52(2): 115 – 121
4. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. *Eur J Anaesthesiol.* 1995;12:265-271.
5. Stamer UM, Maier C, Grond S, Veh-Schmidt B, Klaschik E, Lehmann KA. Tramadol in the management of post-operative pain: a double-blind, placebo- and drug-controlled study. *Eur J Anaesthesiol.* 1997;14:646-654
6. Rodriguez Villamanan JC, Albaladejo BC, Sanchez SA, Carvajal A, Martin AL, Garcia dP. Withdrawal syndrome after long-term treatment with tramadol. *Br J Gen Pract.* 2000;50:406
7. Coetzee JF, van Loggerenberg H. Tramadol or morphine administered during operation: a study of immediate postoperative effects after abdominal hysterectomy. *Br J Anaesth.* 1998;81:737-741.
8. James MFM, Heijke SAM, Gordon PC. Intravenous tramadol versus epidural morphine for postthoracotomy pain relief: a placebo-controlled double-blind trial. *Anesth Analg.* 1996;83:87-91.
9. Raff M. The comparison of continuous intravenous tramadol and morphine sulphate for postoperative analgesia. *Acute Pain.* 1998;1:7-10
10. Bamigbade TA, Langford RM, Blowers AL et al. Pain control in day surgery: tramadol versus standard analgesia [Abstract]. *Br J Anaesth* 1997;80(4)(Suppl 5):558P.

11. Putland AJ, McCluskey A. The analgesic efficacy of tramadol versus ketorolac in day-case laparoscopic sterilisation. *Anaesthesia.* 1999;54:382-385.
12. Bitsch M et al. Obstetric analgesia with tramadol. *Fortschr Med.* 1980;98:632-34
13. Prasertsawat PO et al. Obstetric analgesia: comparison between tramadol, morphine, and pethidine. *Curr Ther Res Clin Exp.* 1986;40:1022—28.
14. Husslein P, Kubista E, Egarter C. Obstetric analgesia with tramadol – Result of a prospective randomized comparison with pethidine. [Geburtshilfliche Analgesie mit Tramadol – Ergebnisse einer prospektiv randomisierten Vergleichsstudie mit Pethidin.] *Z Geburtsh Perinat.* 1987; 191: 234-237.
15. Viegas OAC, Khaw B, Ratnam SS. Tramadol in labor pain in primiparous patients. A prospective comparative clinical trial. *Eur J Obstet Gynecol Reprod Biol.* 1993;49:131-135.
16. Pagliara L, Tornago S, Metastasio J, et al. Tramadol compared with diclofenac in traumatic musculoskeletal pain. *Curr Ther Res.* 1997;58:473-480.
17. Ward ME, Radburn J, Morant S. Evaluation of intravenous tramadol for use in the prehospital situation by ambulance paramedics. *Prehospital Disaster Med.* 1997;12:158-162.
18. Osipova et al. Analgesic effect of tramadol in cancer patients with chronic pain: a comparison with prolonged action morphine sulfate. *Curr Ther Res Clin Exp.* 1991;50:812-21.
19. Wilder-Smith CH, Schimke J, Osterwalder O, Senn H-J. Oral tramadol, a opioid agonist and monoamine reuptake-blocker, and morphine for strong cancer-related pain. *Ann Oncol.* 1994;5:141-146.
20. Grond S, Radbruch L, Meuser T, Loick G, Sabatowski R, Lehmann KA. High-dose tramadol in comparison to low-dose morphine for cancer pain relief. *J Pain Symptom Manage* 1999 Sep;18(3):174-9.
21. World Health Organization. Cancer pain relief: with a guide to opioid availability. Geneva: World Health Organization. 1996.
22. Roth SH. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. *J Rheumatol.* 1998; 25 : 1358-1363.
23. Pavelka K, Peliskova Z, Stehlikova H, Ratcliffe S, Repas C. Intraindividual differences in pain relief and functional improvement in osteoarthritis with diclofenac or tramadol. *Clin Drug Invest.* 1998;16:421-429.

24. Schnitzer TJ, Kamin M, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain: a randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 1999;42:1370-1377

25. Rubinow A. Pain of osteoarthritis and its management. Newsletter of the IASP Special Interest Group on Rheumatic Pain. 1998;1-5.

26. American College of Rheumatology Subcommittee on Osteoarthritis. Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis Rheum.* 2000;43:1905-1915.

27. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol.* 2000;27:772-778.

28. Sorge J, Stadler TH. Comparison of the analgesic efficacy and tolerability of tramadol 100mg sustained capsules for the treatment of chronic low back pain. *Clin Drug Invest.* 1997;14:157-164.

29. Schaffer J, Hagemann H, Holzapfel S, Panning B, Piepenbrock S. Untersuchung zur postoperativen Schmerztherapie bei Kleinkindern mit Tramadol. *Fortschr Anasthesiol.* 1989;3:42-45.

30. Barsoum MW. Comparison of the efficacy and tolerability of tramadol, pethidine and nalbuphine in children with postoperative pain—an open randomised study. *Clin Drug Invest.* 1995;9:183-190.

31. Bosenberg AT, Ratcliffe S. The respiratory effects of tramadol in children under halothane anaesthesia. *Anaesthesia.* 1998;53:960-964.

32. Roelofse JA, Payne KA. Oral tramadol: analgesic efficacy in children following multiple dental extractions. *Eur J Anaesthesiol.* 1999;16:441-447.

33. Chiaretti A, Viola L, Pietrini D, et al. Preemptive analgesia with tramadol and fentanyl in pediatric neurosurgery. *Childs Nerv Syst.* 2000;16:93-100.

34. Goebel H, Stadler T. Treatment of pain due to postherpetic neuralgia with tramadol. *Clin Drug Invest.* 1995;10:208-214.

35. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology.* 1998;50:1842-1846.

36. Sindrup SH, Andersen G, Madsen C, et al. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. *Pain.* 1999;83:85-90.

37. Moore PA, Crout RJ, Jackson DL, Schneider LG, Graves RW, Bakos L. Tramadol hydrochloride: analgesic efficacy compared with codeine, aspirin with codeine, and placebo after dental extraction. *J Clin Pharmacol.* 1998;38:554-560.

38. Wilder-Smith CH, Hill L, Osler W, O'Keefe S. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci.* 1999;44:1107-1116.

39. Primus G, Pummer K, Vucsina F, Meindl N. Tramadol versus metimazole in alleviating pain in ureteral colic. *Urologe.* 1989;28:103-105.

40. Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol.* 2000;6:250-257

41. Biasi G, Manca S, Manganelli S, Marcolongo R. Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo. *Int J Clin Pharmacol Res.* 1998;18:13-19.

42. Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, Stancavage MM, Anderson DL. Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol.* 1997; 35 (4): 361-364

43. Tobias JD. Seizure after overdose of tramadol. *South Med J.* 1997; 90 (8): 826-827

44. Jick H, Derby LE, Vasilakis C, Five D. The risk of seizures associated with tramadol. *Pharmacotherapy* 1998; 18 (3): 607-611

45. Gasse C, Derby L, Vasilakis-Scaramozza C, Jick H. Incidence of first-time idiopathic seizures in users of tramadol. *Pharmacotherapy* 2000; 20 (6): 629-634

46. Gardner SR, Blough D, Drinkard CR, Shatin D, Anderson G, Graham D, Alderfer R. Tramadol and seizures: a surveillance study in a managed care population. *Pharmacotherapy* 2000; 20 (12): 1423-1431

47. Ellmauer S, Dick W, Otto S, Müller H. Perioperative analgesia in the cardiovascular risk patient: A comparison of haemodynamic side effects following eight different opioids. *Anaesthesist* 1994; 43: 743-749.

48. Houmes RJM, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. *Anesth Analg.* 1992; 74: 510-514

49. Vickers MD, Paravicini D. Comparison of tramadol with morphine for post-operative pain following abdominal surgery. *Eur J Anaesthesiol.* 1995;12:265-271.

50. Langford RM, Bakhshi KN, Moylan S, Foster JMG. Hypoxaemia after lower abdominal surgery: Comparison of tramadol and morphine. *Acute Pain* 1998; 1: 7-12.

51. Bosenberg AT, Ratcliffe S. The respiratory effects of tramadol in children under halothane anaesthesia. *Anaesthesia.* 1998;53:960-964.

52. Sacerdote P, Manfredi B, Mantegazza P, Panerai AE. Antinociceptive and immunosuppressive effects of opiate drugs: A structure-related activity study. Br J *Pharmacol.* 1997; 121: 834-840.; Sacerdote P, Bianchi M, Gaspani L, Panerai AE. Effects of tramadol and its enantiomers on Concanavalin-A- induced proliferation and NK activity of mouse splenocytes: Involvement of serotonin. *Int J Immunopharmacol.* 1999; 21: 727-734.; Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai AE. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesth Analg.* 2000; 90: 1411-1414.

53. Wilder-Smith CH, Bettiga A. The analgesic tramadol has minimal effect on gastrointestinal motor function. *Br J Pharmacol. 1997*; 43: 71-75.

54. Wilder-Smith CH, Hill L, Osler W, O'Keefe S. Effect of tramadol and morphine on pain and gastrointestinal motor function in patients with chronic pancreatitis. *Dig Dis Sci.* 1999;44:1107-1116.

55. Staritz M, Poralla T, Manns M, Meyer zum Büschenfelde KH. Effect of modern analgesic drugs (tramadol, pentazocine, and buprenorphine) on the bile duct sphincter in man. *Gut 1986*; 27: 567-569

56. Scott LJ and Perry CM. Tramadol. A review of ist use in perioperative pain. *Drugs* 2000;60(1):139-176.

57. Bamigbade TA, Langford RM. The clinical use of tramadol hydrochloride. *Pain Reviews* 1998;5:155-82.

SECTION 5: ABUSE LIABILITY: PRECLINICAL AND CLINICAL RESULTS

1. Yanagita T. Drug dependence potential of 1-(m-methoxyphenyl)-2-dimethylaminomethyl)-cyclohexan-1-ol hydrochloride (tramadol) tested in monkeys. *Arzneimittelforschung.* 1978;28:158-163.

2. Ren YH, Zheng JW. Influence of tramadol on morphine discriminative behavior in rats. *Acta Pharmacol Sin.* 2000;21(10):924-926.

3. Friderichs E, Felgenhauer F, Jongschaap P, Osterloh G. Pharmakologische Untersuchungen zur Analgesie, Abhängigkeits-und Toleranzentwicklung von Tramadol, einem stark wirkenden Analgetikum. *Arzneimittel.* 1978;28:122-134.

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

5. Kayser V, Besson JM, 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.

6. Villarreal, JE, Seevers, MH. Evaluation of new compounds for morphine-like physical dependence in the rhesus monkey. Expert Report 1968:1-15.

7. Nakamura H, Yokoyama Y, Shimizu M. Quantitative Assessment of jumping behaviour of morphine-like analgesics in mice. *Arch Int Pharmacodyn Ther.* 1983;263:164-176.

8. Miranda HF, Pinardi G. Antinociception, tolerance, and physical dependence comparison between morphine and tramadol. *Pharmacol Biochem Behav.* 1998;61:357-360.

9. Takemori AE. Preclinical assessment of the physical dependence potential of tramadol. Expert Report 1992:1-18.

10. Huber VHP. Psychologische Wirkungsprüfung eines neuen Analgetikums aus der Cyclohexanol-Reihe: ein Beitrag zur Abklärung des psychischen Abhängigkeitspotentials von Tramadol. *Arzneimittel.* 1978;28:189-191.

11. Barth H, Durra S, Giertz H, Goroll D, Flohe L. Long-term administration of the centrally acting analgesic tramadol did not induce dependence or tolerance [abstract]. *Pain.* 1987;4(suppl 4):S231.

12. Preston KL, Jasinski DR, Testa M. Abuse potential and pharmacological comparison of tramadol and morphine. *Drug Alcohol Depend.* 1991;27:7-17.

13. Jasinski, DR, Preston, KL, Sullivan, JT, Testa, M. Abuse potential of oral tramadol. *NIDA Res Monogr Ser.* 1993;132:103.

14. Cami J, Lamas X, Farre M. Acute effects of tramadol in methadone-maintained volunteers. *Drugs.* 1994;47:39-43.

15. Liu ZM, Zhou WH, Lian Z, Ren ZH, Cao JQ, Cai ZJ. Drug dependence and abuse potential of tramadol. *Acta Pharmacol Sin.* 1999;20:52-54.

16. Flohe VI, Arend I, Cogal A, Richter W, Simon W. Klinische Prüfung der Abhängigkeitsentwicklung nach Langzeitapplikation von Tramadol. *Arzneimittel.* 1978;28:213-217.

17. Richter W, Barth H, Flohe L, Gietz H. Clinical investigation on the development of dependence during oral therapy with tramadol. *Drug Res.* 1985;35:1742-1744.

18. Barth H, Durra S, Giertz H, Goroll D, Flohe L. Long-term administration of the centrally acting analgesic tramadol did not induce dependence or tolerance [abstract]. *Pain.* 1987;4(suppl 4):S231.

19. R.W. Johnson Pharmaceutical Research Institute. Protocol TKB/500690. Post-marketing survey in a US population of patients in pain. Available in Appendix 10 of the NDA 20-281 Report (1999). Raritan, NJ: RWJPRI. 1999.

20. R.W. Johnson Pharmaceutical Research Institute. Protocol TKM/500689. Post-marketing survey in a US population of patients in pain. Available in Appendix 10 of the NDA 20-281 Report (1999). Raritan, NJ: RWPRI. 1999.

21. R.W. Johnson Pharmaceutical Research Institute. Protocol TL2/500689. Post-marketing survey in a US population of patients in pain. Available in Appendix 10 of the NDA 20-281 Report (1999). Raritan, NJ: RWPRI. 1999.

22. Jasinski DR. Abuse potential of oral tramadol: initial data analysis. 1992.

SECTION 6: ABUSE RISK: EPIDEMIOLOGICAL DATA AND CASE REPORTS

1. Cossmann M, Wilsmann KM. Effects and side-effects of tramadol: an open Phase IV study with 7198 patients. [Wirkungen und Begleitwirkungen von Tramadol: offene Phase-IV-Prüfung mit 7198 Patienten.] *Therapiewoche* 1987; 37: 3475-3485.

2. Cossmann M, Wilsmann KM. Application of tramadol injection solution (Tramal®) in acute pain: open trial to assess the acute effect and safety after a single parenteral administration. [Anwendung der Tramadol-Injektionslösung (Tramal®) beim akuten Schmerz: offene Prüfung zur Beurteilung der Akutwirkung und der Verträglichkeit bei einmaliger parenteraler Anwendung.] *Münch Med Wochenschr.* 1988; 130: 633-636.

3. Cossmann M, Wilsmann KM. Treatment of prolonged pain: assessment of the efficacy and safety of repeated administration of tramadol (Tramal®) [Behandlung länger andauernder

Schmerzsyndrome: Beurteilung der Wirkung und Verträglichkeit von Tramadol (Tramal®) bei mehrmaliger Gabe]. Muench Med Wochenschr. 1987;129(46):851-54.

4. Wedier MD, Wohltmann D, Brinkmann S. Tramal Postmarketing Surveillance Cohort Study Switzerland. Grunenthal GmbH. 1989.
5. R.W. Johnson Pharmaceutical Research Institute. Protocol TKB/500690. Post-marketing survey in a US population of patients in pain. Available in Appendix 10 of the NDA 20-281 Report (1999). Raritan, NJ: RWJPRI. 1999.
6. R.W. Johnson Pharmaceutical Research Institute. Protocol TKM/500689. Post-marketing survey in a US population of patients in pain. Available in Appendix 10 of the NDA 20-281 Report (1999). Raritan, NJ: RWPRI. 1999.
7. R.W. Johnson Pharmaceutical Research Institute. Protocol TL2/500689. Post-marketing survey in a US population of patients in pain. Available in Appendix 10 of the NDA 20-281 Report (1999). Raritan, NJ: RWPRI. 1999.
8. R.W. Johnson Pharmaceutical Research Institute. Comprehensive ULTRAM Abuse Liability Review and Update. NDA 20 281. Volume 1. 1999.
9. 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.
10. Cicero TJ, Adams EH, Geller A, Inciardi JA, Munoz A, Schnoll SH, Senay EC, Woody GE. Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic product: results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiology and Drug Safety*. 2005.
11. Adams EH et al. A comparison of the abuse liability of tramadol, NSAIDS, and hydrocodone on patients with non-malignant chronic pain. Accepted for publication in *J of Pain and Symptom Management.*
12. Knisely JS, Campbell E, Dawson KS, Schnoll SH,. Ttramadol post-marketing surveillance in health professionals. Drug and Alcohol Dependence. Sep 2002; 68(1):15-22.
13. Food and Drug Administration Center for Drug Evaluation and Research. The scientific evidence for initiating a scheduling action for Ultram (tramadol hydrochloride) under the controlled substances act. 4-28-1998. Drug Abuse Advisory Committee

14. Keup W. Abuse of Tramal® in Germany. Status-quo and developments from 1977 to 2000 [Mißbrauch von Tramal® (Tramadol) in der Bundesrepublik Deutschland. Stand und Entwicklung in den Jahren 1977 bis 2000]. 15. Oktober 2001.
15. National Forensic Laboratory Information System data supplied by the US Drug Enforcement Administration.
16. Litovitz TL et al. 2000 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med. 2001;19(5):337-95.
17. Thomas AN, Suresh M. Opiate withdrawal after tramadol and patient-controlled analgesia. *Anaesthesia* 2000; 55:826-827.
18. Ripamonti C, Fagnoni E, De Conno F. Withdrawal syndrome after delayed tramadol intake. *Am J Psychiatry.* December 2004; 161(12): 2326-2327.
19. Barsotti CE, Mycyk MB, Reyes J. Withdrawal syndrome from tramadol hydrochloride. *Amer J Emerg Med.* 2003; 87-88.
20. Leo RJ, Narendran R, DeGuiseppe B. Methadone detoxification of tramadol dependence. *J Subst Abuse Treat.* 2000; 19(3):297-299.
21. Yates WR, Nguyen MH, Warnock JK. Tramadol dependence with no history of substance abuse. *Am J Psychiatry.* 2001; 158(6):964-964.
22. NEJM article from Jim Phelps
23. Freye E and Levy J. Acute abstinence syndrome following abrupt cessation of long-term use of tramadol: a case study. *Eur J of Pain.* 2000(4): 307-311.
24. Bennet RM, Schein J, Kosinki MR, Hewitt DJ et al. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. *Arthritis Rheum.* 2005 Aug 15; 53(4):519-527.

SECTION 7: CONTROL STATUS

1. United Nations. Single Convention on Narcotic Drugs, 1961; as amended by the 1972 Protocol Amending the Single Convention on Narcotic Drugs, 1961. United Nations. Convention on Psychotropic Substances, 1971.
2. International Narcotics Control Board. Availability of Opioids for Medical Needs. Vienna: United Nations. 1995.

3. World Health Organization. Achieving Balance in National Opioids Control Policy: Guidelines for Assessment:WHO/EDM/QSM/2000.4. Geneva: WHO; 2000.
4. Adams, E.H., "Physicians Knowledge of Scheduling and Its Effect on the Prescribing of Analgesics," Submitted for Publication.

APPENDIX 1: TERMS RELATING TO ABUSE, DEPENDENCE, WITHDRAWAL AND TOLERANCE

1. The Liaison Committee on Pain and Addiction: A Collaborative Effort of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. Definitions Related to the Use of Opioids for the Treatment of Pain: A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. Approved February 2001. Available at http://www.asam.org/.
2. World Health Organization. ICD-10™Vol. 1: International statistical classification of diseases & related health problems. WHO; 1995.
3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington: APA; 1994.
4. World Health Organization. WHO Expert Committee on Drug Dependence. Twenty-eighth report. (Technical Report Series 836). Geneva, Switzerland: WHO, 1993. World Health Organization. Achieving Balance in National Opioids Control Policy: Guidelines for Assessment:WHO/EDM/QSM/2000.4. Geneva: WHO; 2000.

APPENDIX 2: TABULAR OVERVIEW – ABUSE LIABILITY OF TRAMADOL IN HUMAN CLINICAL STUDIES

1. Table 7 of R.W. Johnson Pharmaceutical Research Institute. Comprehensive ULTRAM Abuse Liability Review and Update. NDA 20 281. Volume 1. 1999.

APPENDIX 3: TESS DEFINITIONS RELATING TO CHRONICITY, REASON FOR EXPOSURE, AND MEDICAL OUTCOME

1. Extracted from the Field Definitions of the American Association of Poison Control Centers Toxic Exposure Surveillance System; Effective January 1, 2002 to December 31, 2005. Available at http://www.aapcc.org. Accessed December 29, 2005.

APPENDIX 4: SCIENTIFIC LITERATURE OVERVIEW: CASE REPORTS/PATIENT SERIES ON TRAMADOL ABUSE, DEPENDENCE, AND WITHDRAWAL

1. Reeves RR, Liberto V. Abuse of combinations of carisoprodol and tramadol. *South Med J.* 2001; 94(5):512-514.
2. Yates WR, Nguyen MH, Warnock JK. Tramadol dependence with no history of substance abuse. *Am J Psychiatry.* 2001; 158(6):964-964.
3. Sannerud CA, Gauvin DV, Sapienza FL. Recent trends and patterns of street drug abuse in the United States. *Society for Neuroscience Abstracts.* 2000; 26(1-2):Abs 870-Abs 870.
4. Leo RJ, Narendran R, DeGuiseppe B. Methadone detoxification of tramadol dependence. *J Subst Abuse Treat.* 2000; 19(3):297-299.
5. Freye E, Levy J. Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram R): a case study. *Eur J Pain.* 2000; 4:307-311.
6. Krummen K, Nelson E, Tsipis G, Siegel E, Bottei E. Tramadol abuse in the Cincinnati area. *J Toxicol Clin Toxicol.*1999; 37:647-647.
7. Sachdeva DK, Jolly BT. Tramadol overdose requiring prolonged opioid antagonism. *Am J Emerg Med.* 1997; 15(2):217-218.
8. J&J Ultram Dear Doctor letter advises of seizures and drug abuse. FDC Reports Pink Sheet.1996(08 Apr):T&G 1-T&G 1.X
9. Barsotti CE, Mycyk MB, Reyes J. Withdrawal syndrome from tramadol hydrochloride. *Amer J Emerg Med.* 2003; 87-88.
10. Roider G, Drasch G, Meyer von L, Sachs H. Tramadol as a drug substitution [Tramadol als Drogenersatz]. *Dtsch ApothZtg.* 2000; 140(29):55-58.
11. Meyer FP, Rimasch H, Blaha B, Banditt P. Tramadol withdrawal in a neonate. *Eur J Clin Pharmacol.* 1997; 53(2):159-160.
12. Withdrawal-syndrome after 10 infusions of Tramadol [Entzugssyndrom nach zehn Tramadol (Tramal u.a.)-Infusionen]. *Arznei-Telegramm.* 1997(9):99-99.
13. Abuse of Tramadol [Mißbrauch von Tramadol]. *Arzneimitteltherapie.* 1994; 12(6):90-90.
14. Thomas AN, Suresh M. Opiate withdrawal after tramadol and patient-controlled analgesia. *Anaesthesia* 2000; 55:826-827.
15. Tramadol (Zydol, Tramake, and Zamadol) –CSM/MCA *Curr Probl Pharmacovigil* 1996; 21: 2

16. Ripamonti C, Fagnoni E, De Conno F. Withdrawal syndrome after delayed tramadol intake. *Am J Psychiatry.* December 2004; 161(12): 2326-2327.

17. Rodriguez Villamanan JC, Albaladejo Blanco C, Sanchez Sanchez A, Carvajal A, Arias LM. Withdrawal syndrome after longterm treatment with tramadol. *Br J Gen Pract.* 2000; 50(454):406-406.

18. Aknine X, Varescon-Pousson I, Boissonnas A. Tramadol (Topalgic) dependence. Concerning the case of a former heroin addict. [Dependance au tramadol (Topalgic). A propos d'un cas chez un ancien heroinomane.] *Ann Med Interne.* 2000; 151(Suppl. B):B34-B35.

19. Jensen JB. Dependence after treatment with tramadol [Afhaengighed efter behandling med tramadol]. *Ugeskr Laeg.* 1997; 159(6):785-785.

20. Bozic K, Kelemen A, Misic-Pavkov G, Gvozdenovic S, Gebauer K, Djordjevic S, Drezgic-Vukic S. Seizures associated with Tramadol abuse. *Epilepsia.* 1999; 40(S2):210-210.

21. Robinson GR, Bhawan S. The abuse potential of tramadol. *No journal present.* Ministry of Health. Medical Practitioners, Pharmacists and Drug Treatment Services Staff.

APPENDIX 5: NATIONAL CONTROL STATUS OF TRAMADOL WORLDWIDE

1. Grunenthal.

2. World Health Organization. Pharmaceuticals: Restrictions in Use and Availability: EDM/QSM/2001.3. Geneva: WHO; March 2001.

APPENDIX 1: Terms Relating to Abuse, Dependence, Withdrawal and Tolerance

Appendix 1 contains the terms of addiction, abuse, physical dependence, tolerance as defined by a consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine representing current practice in the US. The WHO definitions are also presented (WHO ECDD 1993, WHO 2000, ICD-10™, DSM IV™) for a global perspective of these terms.

It should be noted that drug dependence, withdrawal syndrome and tolerance are discrete and different phenomena. Drug dependence must be characterized by maladaptive behaviour; withdrawal syndrome and tolerance are physiological adaptations and are not by themselves sufficient to define dependence.

The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine recognize the following definitions and recommend their use.

Addiction

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Physical Dependence

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Tolerance

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Terminology for mental and behavioural disorders due to psychoactive substance use varies and is often used inconsistently. The WHO has attempted to clarify terms used in this context in several publications (WHO ECDD 1993, WHO 2000, ICD-10™, DSM IV™).

APPENDIX 1: Terms Relating to Abuse, Dependence, Withdrawal and Tolerance

Accurate use of terminology is necessary for a scientific analysis of the abuse risk of a psychoactive drug. The terms drug abuse (harmful use), dependence, withdrawal syndrome and tolerance are for example defined by the WHO Expert Committee on Drug Dependence (WHO ECDD 1993) as stated below.

Abuse (harmful use)

"persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice" (p. 6)

"pattern of psychoactive drug use that causes damage to health, either mental or physical" (p. 6)

Drug dependence

"A cluster of physiological, behavioural and cognitive phenomena of variable intensity, in which the use of a psychoactive drug (or drugs) takes on a high priority. The necessary descriptive characteristics are preoccupation with a desire to obtain and take the drug and persistent drug-seeking behaviour. Determinants and the problematic consequences of drug dependence my be biological or social, and usually interact." (p. 5)

The core concept of the WHO definition of drug dependence requires the presence of a strong desire or sense of compulsion to take the drug (drug-seeking behaviour). The WHO Expert Committee on Drug Dependence notes in their 28th report that

"withdrawal syndromes (or physical dependence) and tolerance are merely consequences of drug exposure which, alone, are not sufficient for a positive diagnosis of drug dependence." (p. 4)

Withdrawal syndrome

"After repeated administration of certain dependence-producing drugs, e.g. opioids, barbiturates and alcohol, abstinence can increase the intensity of drug-seeking behaviour because of the need to avoid or relieve withdrawal discomfort and / or produce physiological changes of sufficient severity to require medical treatment." (p. 5)

Tolerance

"a reduction in the sensitivity to a drug following its repeated administration, in which increased doses are required to produce the same magnitude of effect previously produced by a smaller dose.

This increase in dose may be necessitated by changes in the metabolism of the drug, or a cellular, physiological or behavioural adaptation to the effects of the drug." (p. 5)

The ICD-10™ defines three disorders due to psychoactive substance use (1) Harmful Use, (2) Dependence Syndrome and (3) Withdrawal State. These three disorders are defined below.

Harmful Use/Abuse

The term "harmful use" is used in the ICD-10™ and is similar to the more commonly used term of "abuse" in DSM-IV™. The two are similar in that both refer to psychological and social harm resulting from drug use; however, the two differ in that the ICD-10™ definition of harmful use includes health problems due to drug use whereas the DSM-IV™ definition of abuse does not. The ICD-10™ definition of harmful use is as follows:

A pattern of psychoactive substance use that is causing damage to health. The damage may be physical (as in cases of hepatitis from the self-administration of injected psychoactive substances) or mental (e.g., episodes of depressive disorder secondary to heavy consumption of alcohol.)

There must be clear evidence that the substance use was responsible for (or substantially contributed to) physical or psychological harm including impaired judgment or dysfunctional behavior.

The nature of the harm should be clearly identifiable (and specified).

The pattern of use has persisted for at least one-month or has occurred repeatedly within a 12-month period.

The disorder does not meet the criteria for any other mental or behavioral disorder related to the same drug in the same time period (except for acute intoxication).

Dependence

The term "dependence" in the ICD-10™/DSM-IV™ definitions refers both to what others have called physical or physiological dependence (withdrawal/tolerance) and to psychological dependence (impaired control over drug use).

The DSM-IV™ definition is as follows:

Dependence is manifested by the occurrence of three or more of the following symptoms in the same 12 month period:

APPENDIX 1: Terms Relating to Abuse, Dependence, Withdrawal and Tolerance

1) Tolerance, as defined by either of the following:

(a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect.

(b) Markedly diminished effect with continued use of the same amount of the substance;

2) Withdrawal which can occur upon either cessation of use or reduction in dose. Characteristic symptoms include: dysphoria or depression; insomnia; irritability; frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; and increased appetite and weight gain. These symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning;

3) The substance is often taken in larger amounts over a longer period than was intended;

4) There is a persistent desire or unsuccessful efforts to cut down or control abuse;

5) There is a great deal of time spent in activities necessary to obtain the substance, use the substance or recover from its effects;

6) Important social, occupational, or recreational activities are given up or reduced because of substance use and/or;

7) The substance use is continued despite knowledge of having persistent or recurrent physical or psychological problems that are likely to have been caused or exacerbated by the substance.

Since the above DSM-IV™ definition of dependence overlaps to a great extent with the ICD-10™definition, the former was used in both our classification of dependence cases and in our definition of withdrawal symptoms (see below).

Withdrawal State

In DSM-IV™, the criteria for substance withdrawal are:

The development of a substance-specific syndrome due to the cessation of (or reduction in) substance use that has been heavy or prolonged;

The substance-specific syndrome causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

In ICD-10™, withdrawal is based upon symptoms while in DSM-IV™ a diagnosis of withdrawal must also include clinically significant distress or impaired functioning.

Applying Misuse, Harmful Use, and Dependence Criteria to Therapeutic Drugs

One issue is interpretation of those instances when the dose is increased or a medication is taken for a longer period than was originally intended. The appropriate interpretation of, for example, an increase in dosage or difficulty stopping medication use should involve consideration of the motivation underlying the behavior.

APPENDIX 2:

Tabular Overview – Abuse Liability of Tramadol in Human Clinical Studies

Abuse Liability Clinical Studies

(Country)	No Subjects (tram/ref. drug/placebo)	Study Design	Study Duration	Tramadol Dose (mg)	Route of Admin.	Reference Drug and Dose	Variable Evaluated	Results
Subjective, Behavioral and Psychophysiologic Variable Studies								
Healthy Volunteers								
(Germany)	33 (22/--/11)	DB, PL, //, SD, MD	SD phase 36 hours MD phase 4 days	SD phase 50, 100 mg; MD phase 200, 400 mg	p.o.		Euphoria	No significant difference suggestive of euphoria between tramadol and placebo.
(Germany)	12 (12/12/12)	DB, PL, 3-period XO, SD	7 hours	100 mg	p.o.	Tilidine 100 mg/naloxone 8 mg	Euphoria	No significant difference between tramadol and placebo in subscales indicative of a euphoric effect. Scores indicate tramadol and tilidine/naloxone produced a depressant effect.
(Germany)	30 (15/--/15)	DB, PL	1 week	100 mg	i.m		Euphoria, Drug-seeking behavior	No significant difference between tramadol and placebo for any euphoric subscale. Tramadol did not produce drug-seeking effects in normal subjects.
Opiate Addicts								
(U.S.)	6 (6/--/--)	Open-label, ascending-dose	12 hours	10-300 mg/kg	p.o., s.c.		Physical and subjective variables	Produced some morphine like subjective and behavioral effects. Was identified as an opioid-like drug. No reference drug makes results difficult to assess.
(Europe)	32 (16/16/--)	SB, //	5 days	400 mg Day 1, reduced by 100 mg Day 2-4	i.v.	Clonidine 0.15 mg/day i.v. plus 0.15 mg 3 times/day p.o.	Mitigating effects on withdrawal	Tramadol is able to ameliorate symptoms of opiate withdrawal. Superior to Clonidine. Subjects reported an initial unpleasant feeling following tramadol administration
Protocol AA (U.S.)	12 (12/12/12)	DB, PL Latin square XO, SD	24 hours/dose	75, 150, 300 mg	i.m	Morphine 15,30 mg	Subjective, behavioral, and psychophysiological response	Tramadol was not differentiated from placebo at 75 and 150 mg. Tramadol was identified as an opiate at 300 mg, but no other opioid effects were observed.

XO = Crossover; DB = Double-blind; MC = Multi-center; MD = Multiple-dose; NA = not applicable; NS = not specified; // = Parallel; PL = Placebo-controlled; SB = Single-blind; SD = Single-dose

(Continued)

APPENDIX 2:

Tabular Overview – Abuse Liability of Tramadol in Human Clinical Studies

(Continued)

(Country)	No. Subjects (tram/ref. drug/placebo)	Study Design	Study Duration	Tramadol Dose (mg)	Route of Admin.	Reference Drug and Dose	Variable Evaluated	Results
Subjective, Behavioral and Psychophysiologic Variable Studies (continued)								
Opiate Addicts (continued)								
Protocol TAA (U.S.)	12 (12/12/12)	DB, PL Latin square XO, SD	24 hours/dose	175, 350, 700 mg	p.o.	Oxycodone 20, 40 mg	Subjective, behavioral, and psychophysiological response	Tramadol and oxycodone produce a similar profile of effects which were opioid-like. Tramadol had slower onset and longer duration of effects. Lesser abuse potential for tramadol compared to other orally active opioids analgesics. Addicts gain no benefit in dissolving tablets for i v. delivery.
Protocol TAB (U.S.)	6 (5/–/1)	DB, XO, ascending SD	24 hours/dose	300, 450, 600, 750 mg	p.o		NA	Insufficient enrollment.
Dependence Studies, Subjects with Chronic Pain								
(Europe)	213 (213/–/--)	MC, Open-label, MD	3 weeks	100 mg	i.m.		Tolerance and withdrawal after naloxone i.v. 0.8 mg or 1.6 mg after 3 weeks of tramadol	No subject had scores indicative of moderate or severe dependence.
(Europe)	153 (153/–/--)	MC, Open-label, MD	3 weeks	up to 450 mg/day	p.o		Tolerance and withdrawal after naloxone i.v. 1.6 mg or saline after 3 weeks of tramadol	Tolerance to tramadol does not develop.
(Europe)	200 (200/–/--)	MC, Open-label, MD	up to 6 months	NS	p.o.		Withdrawal after saline followed by 1.6 mg naloxone prior to study and naloxone i.v. 1.6 mg every 2 months	No development of dependence even after 6 months of treatment
(Europe)	125 (125/–/--)	MC, Open-label, MD	up to 6 months	up to 400 mg	p.o.		Withdrawal after naloxone i v. 1.6 mg prior to study and every 2 months	Dependence did not develop.

XO = Crossover; DB = Double-blind; MC = Multi-center; MD = Multiple-dose; NA = not applicable; NS = not specified; // = Parallel; PL = Placebo-controlled; SB = Single-blind; SD = Single-dose

(Continued)

APPENDIX 2:

Tabular Overview – Abuse Liability of Tramadol in Human Clinical Studies

(Continued)

(Country)	No. Subjects (tram/ref drug/placebo)	Study Design	Study Duration	Tramadol Dose (mg)	Route of Admin.	Reference Drug and Dose	Variable Evaluated	Results
Dependence Studies, Subjects with Chronic Pain (continued)								
24 month phase	16 (subgroup of 125 above)	Open-label, MD	up to 24 months	up to 400 mg	p o.		Tolerance and withdrawal after naloxone 1 6 mg every 2 months	All not dependent
Protocol TKB (U.S.) 3-day withdrawal phase	52 (36/16/--)	DB, //, MD	3 days	up to 400 mg	p.o.	APAP up to 400 mg ASA/Codeine up to 2.6 g ASA/240 mg Codeine	Withdrawal	During the 3-day withdrawal phase, comparison of WOW scores failed to reveal any significant differences.
Psychomotor Performance								
(Wales)	9 (9/9/--)	DB, 3-period XO, SD	3 hours	50, 100 mg	p o.	Codeine 50 mg	Psychometric tests	No signif. difference for Digit Symbol Substitution Test or Paired Associate Test At 100 mg dose, subjects took longer to complete Stroop Test.
(Germany)	17 (17/--/--)	Open-label, SD	4 hours	75 mg	p.o.		Eye hand coordination; bicycle ergometer	Physical work capacity and psychomotor performance were unaffected by tramadol in this study.

XO = Crossover, DB = Double-blind; MC = Multi-center; MD = Multiple-dose; NA = not applicable; NS = not specified, // = Parallel, PL = Placebo-controlled, SB = Single-blind; SD = Single-dose

APPENDIX 3:

NFLIS Definitions of Chronicity, Reasons for Exposure, and Medical Outcomes

OPERATIONAL DEFINITIONS

Drug exposures are classified as unintentional or intentional. For purposes of this review, only intentional exposures were evaluated.

Reasons for Exposure

The coding options available for the reason for intentional exposures are:

Intentional: If the case involves a purposeful action resulting in an exposure, the following four categories are available for coding:

Suspected suicidal: An exposure resulting from the inappropriate use of a substance for self-harm or manipulative reasons.

Intentional misuse: An exposure resulting from the intentional improper or incorrect use of a substance for reasons *other* than to achieve a psychotropic effect.

Intentional abuse: An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect. All "recreational" use of substances for any effect is included.

Intentional unknown: An exposure that is determined to be intentional but the specific motive is unknown.

Chronicity This field is used to document the chronicity of the exposure. Coding options include:

Acute: A single, repeated, or continuous exposure occurring over a period of eight hours or less.

Acute-or-chronic: A single acute exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period exceeding eight hours (>8). If this option is selected, exposure duration must also be coded. An example is a patient who takes four doses of aspirin a day therapeutically for six weeks, then takes a single overdose. In this case, the exposure duration would be coded >1 month, ≤ 3 months.

Chronic: A continuous, repeated, or intermittent exposure to the same substance lasting longer than eight hours. If this option is selected, exposure duration must also be coded. Examples include: a medication taken repeatedly for more than eight hours; a person exposed continuously to a chemical for greater than eight hours; a worker exposed to a chemical in the workplace intermittently, one day a week, for several months.

Unknown: The duration of the exposure is unknown or not available.

Medical Outcome

Medical outcome is determined based upon all information available at the conclusion of the case. Only one medical outcome can be chosen per case:

Case followed to known outcome: A response in this area is appropriate only if follow-up continues until medical outcome can be documented with reasonable certainty. If the case is followed to a known outcome, one of the following outcomes is to be chosen:

No effect: The patient did not develop any signs or symptoms as a result of the exposure.

Minor effect: The patient exhibited some signs or symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well being and has no residual disability or disfigurement. If this response is selected, the implication is that the patient had clinical effects that were probably related to the exposure. In this case, the clinical effects are coded as well as the duration of the clinical effects.

Moderate effect: The patient exhibited signs or symptoms as a result of the exposure which were more pronounced, more prolonged, or more of a systematic nature than minor symptoms. Usually some form of treatment is indicated. Symptoms were not life-threatening, and the patient returned to a pre-exposure state of well-being with no residual disability or disfigurement. If this response is selected, the implication is that the patient had clinical effects that were probably related to the exposure. In this case, the clinical effects are coded as well as the duration of the clinical effects. (Examples: corneal abrasion, acid-base disturbance, high fever, disorientation, hypotension which is rapidly responsive to treatment, isolated brief seizures which respond readily to treatment.)

Major effect: The patient exhibited signs or symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. If this response is selected, the implication is that the patient had clinical effects that were probably related to the exposure. In this case, the clinical effects are coded as well as the duration of the clinical effects. (Examples: patients requiring intubation and mechanical ventilation, repeated seizures or status epilepticus, ventricular tachycardia with hypotension, cardiovascular instability, cardiac or respiratory arrest, esophageal stricture, disseminated intravascular coagulation.)

Death: The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not occurred. Only those deaths which are determined to be either probably or undoubtedly related to the exposure are coded with this outcome.

Death, indirect report: A reported fatality is coded as "indirect" if no inquiry was placed to the poison center. For example, if the case was obtained from a medical examiner who sends post mortem reports to the poison center or from a newspaper article.

Case not followed to known outcome: In some cases there is no follow-up. The following are the choices provided for these circumstances:

Not followed, judged as nontoxic exposure: No follow-up calls were made to determine the patient's outcome because the substance implicated was nontoxic, the amount implicated was insignificant, or the route of exposure was unlikely to result in a clinical effect.

Not followed, minimal clinical effects possible: No follow-up calls were made to determine the patient's outcome because the exposure was likely to result in only minimal toxicity. (The patient is expected to experience no more than a minor effect.)

Unable to follow, judged as a potentially toxic exposure: The patient was lost to follow-up, refused follow-up, or was not followed, but the exposure was significant and may have resulted in a moderate, major, or fatal outcome.

Other options:

Unrelated effect: The exposure was probably not responsible for the effect.

Confirmed nonexposure: Objective evidence exists that an exposure initially thought to have occurred actually did not occur. For example, if all missing pills are later located, this coding option is chosen. All cases coded as confirmed non-exposure are excluded from TESS data analyses.

APPENDIX 4:

Scientific literature overview: Case reports/patient series on tramadol abuse/dependence/withdrawal

Description of contents	Country	Reference
Three cases of tramadol/carisoprodol used illicitly to obtain psychotropic effects, history of drug abuse	USA	Reeves & Liberto, South Med J. 2001
Case of tramadol dependence, initially pain patient, high tramadol dose (1.5 g/day), seizure, no history of drug abuse	USA	Yates et al., Am J Psychiatry 2001
Mentions reports from pharmacists pointing to rises in tramadol abuse, reports not further quantified or described	USA	Sannerud et al., Society for Neuroscience Abstracts 2000
Case of methadone detoxification of tramadol abuse, high dose (1.5 g)	USA	Leo et al., J Subst Abuse Treat 2000
Withdrawal after long-term use of tramadol in a pain patient (50 – 100 mg/day, stopped abruptly)	USA	Freye & Levy, Eur J Pain 2000
Tramadol abuse in the Cincinnati area	USA	Krummen et al., J Toxicol Clin Toxicol. 1999
Tramadol overdose (5.5g) with abuse suggested by the author as the reason for intake	USA	Sachdeva & Jolly, Am J Emerg Med 1997
115 reports on tramadol abuse and withdrawal effects received by the FDA since launch	USA	Pink Sheet 1996
Case of withdrawal syndrome from cessation of chronic tramadol use	USA	Barsotti et al., Am J Emerg Med 2003
Test results of blood samples taken on behalf of the police for suspected motoring or criminal offences and cases, in which a legal autopsy had been requested by the public prosecutor's office for clarification of the cause of death, 1995 - 1999	Germany	Roider et al., Dtsch ApothZtg 2000
Tramadol withdrawal in a neonate	Germany	Meyer et al., Eur J Clin Pharmacol 1997
Withdrawal syndrome after 10 infusions of tramadol in a pain patient with a history of heroin and alcohol abuse	Germany	Arnei-Telegramm 1997
Dependence on tramadol in a nurse	Germany	Arzneimitteltherapie 1994
Withdrawal after tramadol PCA	UK	Thomas & Suresh, Anaesthesia 2000
5 reports on tramadol drug dependence, 28 reports on withdrawal between 1994 and 1996; 1 case/ 6000 patients	UK	Curr Probl Pharmacovigilance 1996

APPENDIX 4:

Scientific literature overview: Case reports/patient series on tramadol abuse/dependence/withdrawal

Description of contents	Country	Reference
Withdrawal syndrome after delayed tramadol intake in patient with no history of dependence	Italy	Ripamonti et al., Am J Psychiatry Dec. 2004
Withdrawal syndrome after long-term treatment with tramadol; no further symptoms observed after gradual discontinuation of tramadol	Spain	Rodriguez et al., Br J Gen Pract 2000
Tramadol dependence in a former heroin addict, doses between 100 and 1000 mg/day, for feeling of well-being and detachment from daily life	France	Aknine et al., Ann Med Interne 2000
Withdrawal symptoms after abrupt stop of tramadol in 4 pain patients	Denmark	Jensen, Ugeskr Laeg 1997
Seizures associated with tramadol abuse	Czech Republic	Bozic et al., Epilepsia 1999
2 cases of tramadol withdrawal. Street sales, black market theft, prescription forgery pertaining to tramadol have not been observed	New Zealand	Robinson et al.

APPENDIX 5: National control status of tramadol worldwide (according to data available to Grünenthal at the date of this report)

75 countries prescription-only medicine status without psychotropic or narcotic scheduling			**Remarks**
			Mexico 1998: excluded from psychotropic status
			Venezuela 1999: excluded from psychotropic status
			Philippines (Cebu City) 1996: excluded from additional controls
			Colombia 1995: excluded from psychotropic status
29 countries with additional controls, i.e.:	**Psychotropic-like schedule**	**Narcotic schedule**	**Effective date, remarks**
Austria	x		1984, all preparations exempted
Italy	x		1992
CIS[a] -Georgia		x	1997
CIS[a] -rest of CIS countries (11)	x		1993
Bulgaria	x		1999/2001 decrease of level of control: narcotic schedule to psychotropic schedule
Bahrain	x		2000
Brazil		x	1998, codeine-like status
Egypt	x		2000
Jordan		x	2000, codeine-like status
Kuwait	x		
Mauritius	x		2000
Oman	x		1993
Qatar	x		1989
Peru	x		2001
Saudi Arabia	x		1995
South Africa	x		1991
Taiwan	x		1988
Turkey	x		1996

APPENDIX 5: National control status of tramadol worldwide (according to data available to Grünenthal at the date of this report)

29 countries with additional controls, i.e.:	Psychotropic-like schedule	Narcotic schedule	Effective date, remarks
UAE	x		1984

[a] CIS = Commonwealth of Independent States, former USSR - now comprising 12 countries: Armenia, Azerbaijan, Byelorussia, Georgia, Kazachistan, Kyrgyzstan, Moldavia, Russia, Tajikistan, Turkmenistan, Ukraine, Uzbekistan