

Tapentadol

Pre-Review Report

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Summary

Tapentadol is a novel analgesic agent with two mechanisms of action within the same molecule: agonist activity at the μ opioid receptor and norepinephrine reuptake inhibition. Both immediate release and extended release formulations of tapentadol are available and appear to provide analgesia in acute and chronic pain states similar to oxycodone or morphine. Tapentadol demonstrates improved gastrointestinal tolerability (specifically in the incidence of nausea, vomiting, and constipation) compared with strong opioids at doses providing similar analgesia.

Based on the preclinical and clinical pharmacology of tapentadol as well as anecdotal data, the potential for abuse with tapentadol is consistent with currently marketed substances such as hydromorphone, oxycodone, morphine, and tramadol. However, tapentadol has only been marketed since 2008 and therefore has not appeared in many substance use surveys or surveillance reports as of yet limiting the data regarding tapentadol abuse, dependence, diversion, recreation use, or poison control. Overall, the potential toxicity for tapentadol does not appear necessarily greater than that for other μ -opioid agonists and the favourable safety profile represents a clinically significant benefit to subjects especially those in which gastrointestinal adverse events may limit the use of opioids for the relief pain.

1. Substance identification

A. International Nonproprietary Name (INN)

Tapentadol

B. Chemical Abstract Service (CAS) Registry Number

175591-09-0; (Component:175591-23-8)

C. Other Names

3-[(1R,2R)-3-(Dimethylamino)-1-ethyl-2-methylpropyl]phenol Hydrochloride; 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol; BN 200; CG5503; UNII-H8A007M585; R-331333; JNS-024 ER; ChEMBL1201777; AB1008539

D. Trade Names (hydrochloride salt)

Nucynta®; Nucynta® ER (US), Nucynta™ CR (CA), Palexia (BG, CH, CZ, DK, EE, FI, GB, IE); Palexia Depot (DK, FI, SE); Palexia Retard (BG, DE, EE); Palexia SR (GB, IE)

E. Physical properties

Light brown solid.

F. WHO Review History

Tapentadol has not been reviewed previously by the Secretariat at WHO.

2. Chemistry

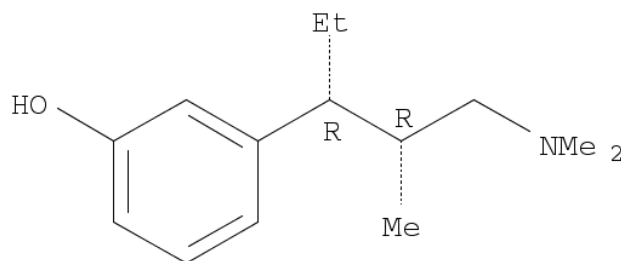
A. Chemical Name

IUPAC Name: 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride

CA Index Name: Phenol, 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]-, hydrochloride

C. Chemical Structure

Free base:



Molecular Formula: C₁₄H₂₃NO

Molecular Weight: 221.3385

Melting point: 209-210 °C

Boiling point: 323.493°C at 760 mmHg;

Fusion point: 134.18 °C (Flash point)

C. *Stereoisomers*

X-ray crystal structure analysis reveals four enantiomers of tapentadol. The crystal structures reveal the stereochemistries at the 3-ethyl and 2-methyl groups to be R,R, S,S, S,R and R,S in stereoisomers (I)-(IV), respectively. The ethyl and aminopropyl groups adopt different orientations with respect to the phenol ring for (I) and (IV) (Ravikumar *et al.*, 2011).

D. *Synthesis*

Tapentadol is synthesized from 1-(3-methoxyphenyl)-1-propanone by a Mannich reaction with dimethylamine hydrochloride to obtain the racemic 3-dimethylamino-1-(3-methoxyphenyl)-2-methylpropan-1-one(13). This intermediary is then subjected to crystallization-induced diastereomer transformation, a Grignard reaction, acylation and finally catalytic hydrogenolysis to give (2R,3R)-2-methyl-3-(3-methoxyphenyl)-N,N-dimethylpentanamine. This synthesis is then followed by deprotection and salt formation for an overall yield of about 52% (Ma *et al.*, 2010).

E. *Chemical description*

Tapentadol is a new synthetic compound. Tapentadol has two chiral centres and is manufactured as a single (R, R) stereoisomer. Tapentadol shares a 3-(3-hydroxyphenyl)propylamino structural fragment with morphine and its analogues.

F. *Chemical properties*

Tapentadol is isolated as the hydrochloride salt. All polymorphic forms of tapentadol are freely soluble within the physiological pH range. Tapentadol is designated as Class 1 (high permeability, high solubility) in The Biopharmaceutics Classification System. Stability data have demonstrated that tapentadol hydrochloride is a stable substance. A retest period of 30 months with storage below 25°C has been approved.

G. *Chemical identification*

No additional information found.

3. Ease of convertibility into controlled substances

There are no data available on the conversion of tapentadol into other controlled substances to date.

4. General pharmacology

The published and unpublished preclinical studies have been exclusively conducted or financially supported by the sponsors and developers of tapentadol (Grünenthal GmbH, Aachen, Germany) or their licensing affiliates in various countries.

4.1. Pharmacodynamics

Neuropharmacology and the effects on the central nervous system

Tapentadol was developed to combine agonist activity at the μ opioid receptor (MOR) with norepinephrine (NE) reuptake inhibition (NRI) for improved analgesic efficacy especially in chronic or neuropathic pain disorders. These two analgesic entities exist in a single nonracemic molecule without active metabolites which leaves the relative contributions of the different mechanisms steady over the course of metabolic transformation and purportedly reduce adverse effects (Tzschentke *et al.*, 2007).

In radioligand binding studies, tapentadol bound to rat MOR, DOR, and KOR with K_i values of 0.096, 0.97, and 0.91 μM , respectively and to human MOR with a K_i value of 0.16 μM . Signalling studies revealed strong agonist activity comparable to morphine in [³⁵S]GTP γ S binding cells that express cloned human μ receptors. In addition to this opioid binding profile, tapentadol inhibited NE reuptake transporters with a K_i of 0.48 μM and serotonin (5-HT) reuptake transporters with a K_i of 2.37 μM for rat. In human recombinant transporter studies, tapentadol produced reuptake inhibition for NE and 5-HT of 8.8 and 5.3 μM , respectively. Other *in vitro* activity for tapentadol included submicromolar interactions with the rat σ_2 binding site and rat M1 and human M1-M5 muscarinic receptors. The follow-up to these additional binding sites revealed weak muscarinic antagonist activity and 5-HT₃ antagonistic activity in guinea pig colon bioassay (Tzschentke *et al.*, 2007).

A proposed advantage of tapentadol as a therapeutic is the NRI activity within the molecular entity and the resultant ability to modulate descending pain pathways. Microdialysis studies in the brain (ventral hippocampus) and spinal cord were performed to address this notion. These microdialysis studies revealed a 450% increase above baseline for extracellular levels of NE and 130% increase above baseline for extracellular 5-HT after the higher dose of 10 mg/kg tapentadol whereas morphine failed to alter either NE or 5-HT extracellular levels in the ventral hippocampus of rats (Tzschentke *et al.*, 2007). In addition, tapentadol increased extracellular spinal norepinephrine levels to 182%, a level similar to that produced by venlafaxine. Tapentadol decreased extracellular spinal 5-HT levels (Tzschentke *et al.*, 2012). Electrophysiology tests in spinal nerve-ligated and sham-operated rats revealed that tapentadol reduced evoked responses of spinal dorsal horn neurons to brush, punctate mechanical and thermal stimuli which were reversed by spinal application of the selective α_2 -adrenoceptor antagonist atipamezole or naloxone. These studies suggest that tapentadol can retain a certain degree of efficacy even after nerve-injury, an improvement over morphine (Bee *et al.*, 2011). Tapentadol demonstrated a dose-related antitussive effect following exposure to ammonia in rats similar to that observed with codeine. Tapentadol inhibited gastrointestinal transit ($\leq 50\%$) and

prostaglandin-induced diarrhoea in mice ($\leq 100\%$) with an efficacy between that of morphine and tramadol (Christoph *et al.*, 2010; Terlinden *et al.*, 2010).

Behavioral tests

Tapentadol has been reported to be effective in a wide range of rodent preclinical antinociception, antihyperalgesic, and anti-allodynic assays with a potency slightly less than morphine: hot-plate (~2-3X less potent); tail flick (~2X less potent); writhing (~1.5X less potent); Randall Selitto (2X less potent); mustard oil visceral pain (~1.5-4X less potent in various allodynia tests); spinal nerve-ligation (~2X less potent than morphine) and chronic constriction injury (~2X less potent); streptozotocin model (~3X less potent); formalin test (~equipotent); carrageenan-induced inflammation test (~equipotent); Complete Freund's Adjuvant induced tactile hyperalgesia (~equipotent); and knee joint arthritis (~1.5X more potent). The effects of tapentadol were blocked or partially blocked by both naloxone and yohimbine (completely blocked by a combination of both) but not ritanserin (Christoph *et al.*, 2010; Schiene *et al.*, 2011; Schroder *et al.*, 2010; Tzschentke *et al.*, 2007). Tapentadol maintained a reduced antinociceptive and antihyperalgesic efficacy in OPRM1, μ -opioid receptor knockout mice that was blocked by yohimbine (Kogel *et al.*, 2011). Two papers using isobolographic analysis reveal a synergistic interaction between the μ opioid receptor activity and NRI of tapentadol using $\alpha 2$ antagonist yohimbine and opioid antagonist naloxone (Schroder *et al.*, 2011; Schroder *et al.*, 2010). The results of these studies demonstrate a strong synergy between the μ opioid receptor activity and NRI. This synergy explains the observation that tapentadol possesses a 50-fold lower affinity for MOR yet is only approximately 2-3 fold less potent most behavioral assays.

In experiments by the sponsor and reported in the New Drug Application, tapentadol substituted fully for morphine-trained rats. No substitution was observed in amphetamine-trained rats. A dose of 2.15 mg/kg tapentadol produced conditioned place preference which was blocked by naloxone. Locomotor sensitization was not observed at any doses of tapentadol during the conditioned place preference experiment. Tapentadol (0.01-0.3 mg/kg/infusion) was self-administered by rhesus monkeys trained to self-administer morphine (0.03 mg/kg/infusion).

Interactions with other substances and medicines.

Tapentadol increased the duration of barbiturate-induced anaesthesia in mice in a dose related manner although it was less potent than tramadol. Combination treatment of tapentadol with diazepam or tetrazepam attenuated the muscle-relaxing activity of the latter compounds in mice, measured as a reduction in the incidence of the effect, the duration of relaxation and the relaxation score. Equi-analgesic combinations of pregabalin and tapentadol in rats revealed a synergistic interaction for hyperalgesia in a mouse diabetic neuropathic pain model while combination of pregabalin with morphine or oxycodone only resulted in additive interactions. The combined involvement of three different mechanisms, i.e. μ -opioid receptor agonism and NRI by tapentadol and the $\alpha 2\delta$ subunit modulation by pregabalin is suggested to be the molecular basis of the observed synergistic interaction (Christoph *et al.*, 2010). Indeed, a number of patents are pending for medication combinations of tapentadol and pregabalin or tapentadol and NSAIDs.

4.2. Routes of administration and dosage

Tablet, oral: Nucynta® or Palexia® IR: 50 mg, 75 mg, 100 mg

Tablet, extended release, oral: Nucynta[®]ER or Palexia[®]SR: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg

4.3. Pharmacokinetics

After oral administration, tapentadol is rapidly and completely absorbed with peak serum levels reached within 1.25 hours and within 3-6 hours for the long acting formulations. Plasma protein binding of tapentadol is approximately 20% and the protein binding is independent of substance concentration. Mean absolute bioavailability is ~32% after a fasting single-dose administration of tapentadol (Terlinden *et al.*, 2007; Tzschentke *et al.*, 2007). The half-life elimination is 4 hours for the immediate release formulation and 5-6 hours for the long-acting formulations.

Tapentadol undergoes extensive metabolism, including first pass metabolism. Tapentadol is metabolized primarily via phase 2 glucuronidation to tapentadol-O-glucuronide and metabolized to a lesser degree by CYP2C9 and CYP2C19 to desmethyl tapentadol (13%), and CYP2D6 to hydroxytapentadol (2%) (Terlinden *et al.*, 2010; Terlinden *et al.*, 2007). In-vitro studies did not reveal a potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. All the tapentadol metabolites are pharmacologically inactive and the parent molecule appears to be the only active molecule (Tzschentke *et al.*, 2007). This profile reduces the probability of large individual variations in the pharmacological effects of tapentadol. Tapentadol is excreted in the urine (99%: 70% conjugated metabolites; 3% unchanged substance)

There is no clinically relevant difference in the pharmacokinetics of tapentadol in men and women and exposure to tapentadol is similar for young adult (18 years to 45 years of age) and elderly (≥ 65 years of age) subjects. Exposure and peak serum concentrations of tapentadol were increased in subjects with mild or moderate hepatic impairment, whereas the maximum concentrations of the metabolite, tapentadol-O-glucuronide, were decreased in subjects with moderate liver impairment. In subjects with mild, moderate and severe renal impairment, the AUC ∞ of tapentadol-O-glucuronide was 1.5-fold, 2.5-fold and 5.5-fold higher as compared to subjects with normal renal function, respectively. No clinical studies were conducted to directly compare the effects of race on the pharmacokinetics of tapentadol. However, in healthy Japanese men, the pharmacokinetics of tapentadol is similar to that observed in the Phase I data (HP5503/48). The population pharmacokinetic model predicted that the clearance of tapentadol in Black, Hispanic-Latinos and other combined non-Caucasian racial groups was approximately 17%, 11% and 15% lower, respectively, compared to that predicted in Caucasian subjects. Therefore, the effect of race on tapentadol pharmacokinetics is of little clinical relevance.

5. Toxicology

The toxicity profile of tapentadol from safety tests is similar to other opioid analgesics or tramadol. In experiments reported by the sponsor in the New Drug Application (NDA 22-304), a dose-related increase in emetic episodes was observed in ferrets with tapentadol but less frequently than morphine. Respiratory depression (bradypnea, changes in blood gas levels, irregular breathing, reduced respiratory volume) was observed in rats, rabbits and dogs, at 0.7-3x maximum clinical exposure (C_{max}). Tolerance to respiratory depression developed at a similar rate as morphine. A multi-species effect on the cardiovascular system was observed, including QT interval prolongation in conscious dogs. Heart rate and blood pressure were increased in conscious rats and dogs in a dose-related manner and tachycardia

and atrioventricular block were observed at all doses in dogs. In contrast, blood pressure was decreased in anaesthetised rabbits and dogs consistent with opioid-related cardiovascular depressant activity. Convulsions were observed in rats at doses around 11x the clinical C_{max} and an increased incidence of pentylenetetrazole-induced convulsions occurred at tapentadol doses above 2 mg/kg IV. Pre-treatment with diazepam or phenobarbital prevented tapentadol induced convulsions while naloxone had a variable effect on blocking tapentadol's effects on these endpoints. Effects on female fertility, embryofetal development, teratogenicity and postnatal survival were observed in test species, mostly associated with maternotoxicity. Tapentadol was not genotoxic *in vivo* when tested up to the maximum tolerated dose using the two endpoints of chromosomal aberration and unscheduled DNA synthesis. Long-term animal studies did not identify a potential carcinogenic risk relevant to humans.

In summary comments from their reports on tapentadol (NDA 22-304; ASPAR-Palexia), evaluators expressed concern that the achieved animal/human exposure margins in the toxicity studies were low due to dose-limiting toxicity, particularly in the CNS, thereby restricting the capacity of the toxicity studies to fully assess the safety of tapentadol. However, their concern of potential toxicity for tapentadol was not necessarily greater than that for other μ -opioid agonists. Therefore, the safety assessment of tapentadol will rely primarily on the clinical data as it is collected in post-surveillance marketing surveys.

6. Adverse reactions in humans

Currently, the adverse reactions in humans are predominantly reported in clinical trials (Daniels *et al.*, 2009a; Hale *et al.*, 2009; Hartrick *et al.*, 2009; Jeong *et al.*, 2012; Vorsanger *et al.*, 2011). In an analysis of the Phase II/III Multiple-dose Double-blind studies, the percentage of subjects with at least one treatment emergent adverse events (TEAE) was higher in the tapentadol IR group (71.9%) compared with the placebo group (47.8%) and was lower in the tapentadol IR group (71.9%) compared with the oxycodone IR group (84.0%). The most commonly reported (by $\geq 5\%$ of subjects) TEAEs in the tapentadol IR group were nausea, dizziness, vomiting, somnolence, headache, constipation and pruritus. The percentage of subjects with TEAEs relating to gastrointestinal disorders (nausea, vomiting and constipation) and with dizziness was lower in the tapentadol IR group compared with the oxycodone IR group and the percentage of subjects with somnolence or headache was similar between the two groups. The overall adverse event profile is for tapentadol was similar to oxycodone for short-term treatment (up to 10 days of treatment) and prolonged treatment, except withdrawal symptoms. The only cases of withdrawal syndrome and withdrawal syndrome with tapentadol IR were seen in KF5503/34 and were mostly classified as mild.

With regards to study discontinuation due to tapentadol, there were two subjects with TEAEs leading to discontinuation and the most commonly reported TEAEs were nausea (6.6%) and headache (5.2%) in the Phase III Open-label Extension Safety Analysis Set. All other TEAEs were reported in $< 5\%$ of subjects. In the Phase II/III multiple-dose double-blind studies, 2.2% of placebo-treated subjects, 10.1% of tapentadol IR treated subjects, and 16.7% of oxycodone IR treated subjects discontinued study participation prematurely because of TEAEs (Vorsanger *et al.*, 2010).

To address the potential risk of adverse events in patients receiving tapentadol, Janssen Pharmaceuticals developed and recently distributed Risk Evaluation and Mitigation

Strategies (REMS) in August 2011 for NUCYNTA® (<http://www.fda.gov/downloads/Drugs/DrugSafety/UCM176364.pdf>) and NUCYNTA® ER (tapentadol) tablets <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM270268.pdf>).

7. Dependence potential

Little published preclinical data on dependence potential for tapentadol exists. In a chronic constriction injury model in rats, tolerance developed to the anti-allodynic effects of 6.81 mg/kg morphine after 10 days and 6.81 mg/kg tapentadol after 23 days (Tzschentke *et al.*, 2007). Because morphine is twice as potent as tapentadol in this assay, it is unclear if equally effective treatment doses were used and therefore whether tolerance develops at similar rates to these opioids morphine and tapentadol. Nevertheless, tolerance and dependence did develop to tapentadol in these rats.

Withdrawal from tapentadol was best described in a clinical study using flexible doses of 50 or 100 mg every 4-6 hours as needed over a 90 day period in patients with low back pain or knee/hip osteoarthritis (Hale *et al.*, 2009). Patients were assessed for withdrawal during the trial and at the end of the study when tapentadol was removed without taper. Patients taking tapentadol were less likely to have withdrawal symptoms using the Clinical Opiate Withdrawal Scale than subjects taking oxycodone (17% vs. 29%) although no differences were found using the Subjective Opiate Withdrawal Scale between tapentadol and oxycodone. Although withdrawal syndrome was reported in 1% of either of the tapentadol and oxycodone groups, only one subject reported a serious adverse event consisting of elevated systolic blood pressure, irritability, and anxiety after receiving treatment of 250-600 mg total daily dose of tapentadol. Currently, additional clinical trials are evaluating the potential for withdrawal from tapentadol post-trial in patients with painful diabetic peripheral neuropathy or osteoarthritis and low back pain (NCT01041859; NCT00487435), but the results of these studies have not been released.

8. Abuse potential

In clinical abuse liability studies, tapentadol (50-200 mg) was compared to hydromorphone (4-16 mg) in opioid-experienced, nondependent subjects in a single-dose, double blind, double-dummy, placebo-controlled, randomized, crossover study (Study HP5503/14). All tapentadol and hydromorphone doses produced dose-dependent, significant Overall Drug 'Liking' on the VAS scale, decreased pupil diameter, and decreased visual-motor coordination as measured by Choice Reaction Time and Divided Attention Tasks at the higher doses. These effects reached their highest value 1-2 hours after dosing and were not different from the calculated equally analgesic doses of hydromorphone IR. Other results for tapentadol as compared to hydromorphone, 'Any Drug Effect' (VAS), Subjected-Rated Opioid Agonist Scale, and Observer-Rated Single-Dose Questionnaire, were consistent with the above findings.

Over evidence for potential abuse of tapentadol has been reported in completed and ongoing clinical trials. In the Phase 3 clinical studies (10 day – KF5503/33; 90 day – KF5503/34; 9 day open label extension period – KF5503/32) a small number of patients that were experienced opioid users self-administered more tapentadol IR (up to 1200 mg/day) although this did not result in adverse events. A clinical trial recently completed in February 2012 (Study NCT01545778) but without published results, examines the potential risk of shopping behaviour for tapentadol IR compared to oxycodone IR. Shopping behaviour was defined as

patients with prescriptions with at least one day of overlap, written by ≥ 2 different prescribers and filled in 3 or more pharmacies (Cepeda *et al.*, 2012).

Over the past two years, only a few reports on tapentadol from internet websites devoted to sharing information and experiences on substance use and abuse have appeared (<http://www.drugs-forum.com/>, <http://forum.opiophile.org/forum.php>, <http://www.erowid.org/>). The majority of the reports about tapentadol are informational including available doses, formulations, and effects, some techniques for injecting tapentadol IR, the difficulties of breaking down the tapentadol ER tablet, and the warnings not to snort or smoke crushed tapentadol due to severe burning. There is disagreement among the postings on whether or not the tapentadol experience is worth experiencing. Representative comments about tapentadol include: “pretty decent euphoria;” “more sedative and much stronger than ultram;” “not as euphoric as oxy;” “opiate warmth in your legs and body;” “led to a wonderful relaxed meditation and took all the edginess away from the adderall comedown;” “I watched my friend take this shot, and he was blown away by the rush;” and, “I have eaten, snorted, IV'd and IM'd them and noticed a serious disappointment.”

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Clinical trial studies indicate that tapentadol is an effective analgesic for a range of pain conditions with efficacy similar to comparison doses of either oxycodone or morphine but with lower incidences of adverse gastrointestinal events (Jeong *et al.*, 2012; Vadivelu *et al.*, 2011; Wade *et al.*, 2009). The efficacy of tapentadol IR for the relief of moderate to severe acute pain was demonstrated in both in-patient and out-patient settings and in both visceral and somatic pain conditions such as bunionectomy (Daniels *et al.*, 2009a; Daniels *et al.*, 2009b; Stegmann *et al.*, 2008)), end-stage degenerative knee or hip joint disease (Etropolski *et al.*, 2011; Hale *et al.*, 2009; Hartrick *et al.*, 2009), and hysterectomy (Study KF5503/35). Tapentadol ER provided effective analgesia for patients with chronic osteoarthritis and low back pain (Afilalo *et al.*, 2010; Etropolski *et al.*, 2010; Lange *et al.*, 2010) and pain associated with diabetic peripheral neuropathy (Schwartz *et al.*, 2011; Steigerwald *et al.*, 2012). Neuropathic pain states are often discussed in reviews of tapentadol's clinical efficacy with the hope that the two potentially synergistic mechanisms of opioid agonism and NRI will be an improvement for tapentadol over analgesics with just a single mechanism of action (Hartrick *et al.*, 2012; Hoy, 2012; Pierce *et al.*, 2012). A clinical trial with a combination of tapentadol with pregabalin for neuropathic pain or low back pain is currently underway (NCT01352741) to investigate an additional third mechanism to alleviate pain.

10. Listing on the WHO Model List of Essential Medicines

Tapentadol is not listed in the 17th edition of WHO Model List of Essential Medicines (March 2011).

11. Marketing authorizations (as a medicine)

Ortho-McNeil-Janssen Pharmaceuticals, Inc. licenses marketing rights for tapentadol from Grünenthal for the United States, Canada and Japan. Johnson & Johnson Pharmaceutical Research & Development, L.L.C. markets tapentadol extended/prolonged-release in the United States and Canada. Janssen Pharmaceutica N.V. has a licensing agreement with Grünenthal to register, manufacture and commercialize tapentadol to selected Asia Pacific, Latin American, African, and New European countries including Turkey and Greece, under

Grünenthal's NUCYNTA® /PALEXIA® trademark for both the immediate- and prolonged-release formulations. In total, Janssen has the right to market tapentadol in more than 80 additional countries. While Janssen and Grünenthal each manufacture tapentadol for certain regions, Janssen is responsible for marketing, distributing, promoting and selling tapentadol in the entire licensed territory.

12. Industrial use

None

13. Non-medical use, abuse and dependence

Some data on non-medical use, abuse and dependence of tapentadol for the first 18 months following its launch in June 2009 has been collected by the four different programs within Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System. and reported at the American Academy of Pain Medicine's 2012 Annual Meeting. From July 2009 through December 2010, the number of unique recipients of dispensed drug (URDD) per quarter increased by more than 70,000. Although the URDD for tapentadol IR increased during this period, the diversion rate for tapentadol IR calculated per 1,000 URDD remained low and did not change significantly. The diversion rate for tapentadol IR was comparable to that of tramadol and notably lower than that of oxycodone and hydrocodone. From data collected in the Opioid Treatment Program, the rate of patients entering opioid treatment programs with tapentadol IR abuse per 100,000 population was stable over time, comparable to the rate for tramadol and low relative to the rates for oxycodone and hydrocodone. The highest opioid treatment program rate per 1,000 URDD for tapentadol IR was observed shortly after tapentadol IR first became available, in the fourth quarter of 2009 (Dart *et al.*, 2012a). The non-medical use of tapentadol IR among US college students during the first 21 months after tapentadol IR was reported by 0.8% (93/11,777) students with majority of non-medical users of tapentadol IR being multi-substance users. The primary route of tapentadol IR administration was oral (swallowed or chewed), followed by inhalation (smoked or snorted). However, non-medical tapentadol IR use has been decreasing over time from the fourth quarter of 2009 through the first quarter of 2011 suggesting that the peak in fourth quarter of 2009 were multi-substance users who may have been experimenting with tapentadol IR (Dart *et al.*, 2012a; Dart *et al.*, 2012b). Taken together to date, the results from the different RADARS System programs indicate that tapentadol IR is creating less public health burden (e.g., arrests, admissions to public detoxification programs, calls to poison centers) than oxycodone and hydrocodone. At the current time, within 5 years of tapentadol's launch, the analyses of tapentadol IR data shows lower abuse than oxycodone and slightly higher abuse than tramadol. Despite the increasing availability of tapentadol IR, rates of abuse have remained relatively stable.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

As a new medicine, tapentadol use is still very low. Tapentadol is primarily prescribed and dispensed on an out-patient basis for osteoarthritis, joint pain or chronic pain states that have not responded to other medicines. Most hospital formularies are only recently listing tapentadol. Data on the incidences of overdose for tapentadol alone is unavailable although two reports of overdose death from multiple substance use including tapentadol have been reported (Coroner's Report, California and Alabama, USA <http://www.cal-tox.org/resourcefiles/Tapentadol%20CAT.pdf>). Tapentadol has not been included directly

in the questionnaires for the Monitoring the Future Survey 2012 or appeared in SAMHSA's 2010 National Survey on Drug Use and Health, California Poison Control System, Drug Abuse Warning Network 2009, or Community Epidemiology Work Group 2011. Therefore, at the current time, data on the magnitude of public health problems related to misuse, abuse and dependence is minimal.

15. Licit production, consumption and international trade

The Grünenthal Group in its licensing agreement with Janssen Pharmaceutica N.V. and Johnson & Johnson Pharmaceutical Research & Development L.L.C. can manufacture and trade tapentadol in selected countries such as United States, Canada, Japan, Africa, Turkey, Greece, and other Asia Pacific and Latin American countries, under Grünenthal's PALEXIA® /PALEXIS® /NUCYNTA® trademark for both the immediate- and prolonged-release (IR /PR) formulations. Companies that are currently manufacturing tapentadol include Hangzhou Uniwise International Co., Ltd (Zhejiang, China), Beijing HuiKang BoYuan Chemical Tech Co., Ltd. (Beijing, China), Jai Radhe Sales (Ahmedabad, India), and Farmaceutici Formenti, S.p.A. (Milano, Italy).

Since its release, the final aggregate production quotas for tapentadol in the USA from the Federal Register (74 FR 23881) were as follows: 2010 - 1,000,000 g; and, 2011 - 403,000 g. The estimated quotas for 2012 are 5,400,000 g suggesting an increased demand in the past year. These estimates do not include tapentadol that will be imported from other countries to the USA.

16. Illicit manufacture and traffic and related information

No information or evidence available for illicit manufacture or trafficking.

17. Current international controls and their impact

No current international controls under any of the international drug control conventions.

18. Current and past national controls

US Department of Justice, Drug Enforcement Administration (21 CFR Part 1308) placed tapentadol into Controlled Substances Schedule II on June 22, 2009. The US Food and Drug Administration's Center for Drug Evaluation and Research suggests that the data obtained during clinical development indicates the abuse, misuse, and diversion of tapentadol IR are likely to be extremely high and the effective management of these risks postmarketing are recommended (NDA 22-304 CSS review 10-17-2008). Indeed, Risk Evaluation and Mitigation Strategies have been developed for both tapentadol IR and ER (see above). Australian Public Assessment Record by Therapeutic Goods Administration has proposed that tapentadol be scheduled as S8 and The Expert Advisory Committee on Drugs of the New Zealand Ministry of Health has considered tapentadol under its Misuse of Drugs Act 1975. The United Kingdom classifies tapentadol as a controlled substance under Schedule 2 (Class A) to the Misuse of Drugs Act 1971.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Additive effects between the concomitant use of tapentadol and other opioid receptor agonist analgesics, selective serotonergic reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, general anaesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol and illicit substances) have not been systematically studied. Even though there is no evidence from the current clinical data, interactive effects could occur due to the pharmacological actions of tapentadol, potentially resulting in respiratory depression, hypotension, profound sedation or coma.

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