

Tapentadol

Critical Review Report

Agenda item 4.1

Expert Committee on Drug Dependence
Thirty-sixth Meeting
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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 and may provide a new therapeutic for the relief of neuropathies.

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 drugs such as hydromorphone, oxycodone, morphine, and tramadol. Tapentadol has been marketed since 2008 without significant events or signs of abuse and currently is dispensed with tamper-resistant coatings. However, tapentadol has not appeared in many drug use surveys or surveillance reports as of yet which limits the data regarding tapentadol abuse, dependence, diversion, recreation use, or poison control. Those data available suggest the potential for abuse of tapentadol to be similar to other μ -opioid agonists or slightly less. 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® (US); Nucynta® IR (CA); Nucynta® ER (CA, US); Palexia® (AT, AU, BE, BG, CH, CY, CZ, DE, DK, EC, EE, EL, ES, FI, FR, IE, IS, IT, LT, LU, LV, MT, MX, NL, NO, PL, PT, RO, SE, SI, SK, UK); Palexia® retard (AT, BE, BG, CH, CZ, DE, EC, EL, EE, ES, LT, LU, LV, MT, MX, NL, PL, PT, RO, SK); Palexia® depot (DK, FI, IS, NO, SE); Palexia® LP (FR); Palexia® SR (AU, IE, SI, UK); Palexias® (HU); Palexis® (BR, CL, CO CR); Palexis® ER (BR); Palexis® retard (CL, CO, CR); Tapentadol Grünenthal (DE); Tapentadol Grünenthal retard (DE); Yantil® (DE, BE, ES, IT, LU, NL); Yantil® retard (DE, BE, ES, LU, NL)

E. *Street names*

F. *Physical properties*

Light brown solid.

G. *WHO Review History*

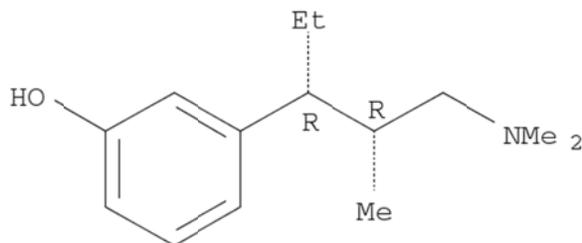
Tapentadol was pre-reviewed during the 35th meeting of ECDD and a recommendation was made for critical review.

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

B. 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)⁽¹⁾.

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%⁽²⁾. Improved yields are proposed using a key step of alkylation of the ketone intermediate of (S)-1-(3-methoxyphenyl)-2-methyl-3-[methyl(phenylmethyl)amino] -1-propanone to yield the compd. of α -ethyl-3-methoxy- α -[1-methyl-2-[methyl(phenylmethyl)amino] ethyl]benzenemethanol with high stereoselectivity due to the presence of the benzyl group as substituent of the amino group^(3,4).

E. Chemical description

Tapentadol is a 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

Most 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⁽⁵⁾.

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⁽⁵⁾.

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⁽⁵⁾. 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⁽⁶⁾. 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 opioid antagonist naloxone. These studies suggest that tapentadol can retain a certain degree of efficacy even after nerve-injury, an improvement over morphine⁽⁷⁾. 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^(8, 9).

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 - 3 X less potent); tail flick (~ 2 X less potent); writhing (~ 1.5 X less potent); Randall Selitto (2 X less potent); mustard oil visceral pain (~ 1.5 - 4 X less potent in various allodynia tests); spinal nerve-ligation (~ 2 X less potent than morphine) and chronic constriction injury (~ 2 X less potent); streptozotocin model (~ 3 X less potent); formalin test (\sim equipotent); carrageenan-induced inflammation test (\sim equipotent); Complete Freund's Adjuvant induced tactile hyperalgesia (\sim equipotent); and knee joint arthritis (~ 1.5 X 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^(5, 8, 10, 11). Tapentadol produced a reduced antinociceptive and antihyperalgesic efficacy in OPRM1, μ -opioid receptor knockout mice that was blocked by yohimbine⁽¹²⁾. Two papers using isobolographic analysis reveal a synergistic interaction between the μ opioid receptor activity and NRI of tapentadol using α 2 antagonist yohimbine and opioid antagonist naloxone^(11, 13) which is probably due to an enhanced CSF concentrations of norepinephrine synergistically contributing to the effects of opioid actions^(6, 14). A lack of synergy, i.e., simple additivity, was observed for these combined mechanisms of tapentadol for gastrointestinal transit⁽¹⁵⁾. Overall, the results of these studies demonstrate a strong synergy between the μ opioid receptor activity and NRI and support the clinical observations outlined below. 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 behavioural assays.

Interactions with other drugs 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 α 2 δ subunit modulation by pregabalin is suggested to be the molecular basis of the observed synergistic interaction⁽⁸⁾. 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, immediate release, oral: 50 mg, 75 mg, 100 mg

Tablet, extended release, oral: 25 mg, 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 drug concentration. Mean absolute bioavailability is ~32% after a fasting single-dose administration of tapentadol^(5, 16). The half-life elimination is 4 hours for the immediate release formulation and 5-6 hours for the long-acting formulations. The absolute bioavailability for both tapentadol IR and tapentadol PR was ~ 32% under fasted conditions⁽¹⁷⁾ and coadministration of the 250 mg dose with a high-fat meal increased C_{max} and AUC values by an average of less than 17%⁽¹⁸⁾. Overall, the AUC for tapentadol PR was very similar to tapentadol IR although C_{max} was lower and the half-value duration and mean residence times were longer for the prolonged-release formulation⁽¹⁷⁾.

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%)^(9, 16). 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⁽⁵⁾. 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 drug)

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 clinically significant differences were observed in the pharmacokinetics of tapentadol between Japanese and Caucasian subjects⁽¹⁸⁾. 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 small.

5. Toxicology

The toxicity profile of tapentadol from safety tests is similar to other opioid analgesics. 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 this was less frequent than with 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}), indicating an opioid-like respiratory depression. The respiratory depressive potency of tapentadol was lower than that of morphine. Tolerance to respiratory depression developed at a similar rate as morphine.

High doses of tapentadol IV resulted in transient increases of heart rate and arterial blood pressure in conscious rats and dogs, and decreased blood pressure in anesthetized rabbits and dogs consistent with opioid-related cardiovascular depressant activity. At very high concentrations, tapentadol induced a delay of cardiac repolarisation in-vitro concentrations. Non-persistent prolongations of the QTc time were observed in dogs in repeat dose toxicity studies. In safety pharmacology studies with repeated ECG measurements, tapentadol did not show any prolongation of heart rate corrected QTc times in rabbits and in dogs at exposures more than 12-times the C_{max} seen after doses equivalent to therapeutic doses in humans. In contrast, blood pressure was decreased in anaesthetised rabbits and dogs consistent with opioid-related cardiovascular depressant activity.

Direct convulsant effects were observed in rats at very high doses around 11x the antinociceptive dose range. Proconvulsant effects were observed in the upper antinociceptive range in animals with pentylenetetrazole-induced lowered thresholds. Pre-treatment with diazepam, phenobarbital, and naloxone prevented tapentadol induced convulsions. Effects on female fertility, embryofetal development, teratogenicity and postnatal survival were observed in test species, mostly associated with maternotoxicity. Tapentadol was evaluated in a battery of mutagenicity tests, comprising an Ames test, two in vitro chromosome aberration tests, one ex-vivo unscheduled DNA synthesis test, and an in-vivo chromosomal aberration test. There was one positive in-vitro mutagenicity test that was not regarded as a signal of potential risk to humans with regard to genotoxicity. Long-term animal studies did not identify a potential carcinogenic risk relevant to humans.

In summary comments from their technical reports on tapentadol (NDA 22-304; Australian Therapeutic Goods Association 2011), 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 continues to rely primarily on the clinical data as it is collected in post-surveillance marketing surveys.

6. Adverse reactions in humans

Currently, a broad clinical development program including approximately 14,000 patients/subjects and post-authorization experience with an estimated exposure of 120 million Patient Treatment Days has been used to evaluate the adverse effect profile of tapentadol.

Adverse reactions in humans are predominantly reported in clinical trials⁽¹⁹⁻²³⁾. 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 $\geq 10\%$ of subjects) TEAEs in the tapentadol IR group from doses ranging from 50 to 100 mg were nausea, dizziness, vomiting, somnolence, headache and reported as of mild or moderate intensity. 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 incidence of nausea and vomiting decreased with time although constipation remained at the same level over prolonged used. 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.

For tapentadol PR, the most common adverse drug reactions ($\geq 10\%$ subjects) observed with tapentadol PR treatment in the dose range of 50 mg to 250 mg twice daily were nausea, dizziness, somnolence, headache, and constipation (KF5503/24). In a multiple studies, the incidence of TEAEs were significantly lower with tapentadol PR than oxycodone CR⁽²⁴⁾.

Based on pooled data from Phase II and Phase III multiple dose trials in non-cancer pain, 18% of the subjects on tapentadol PR discontinued due to TEAEs (gastrointestinal events, general disorders, nervous system disorders, and skin disorders) which was markedly lower than with oxycodone CR (37%) with the difference particularly notable in the titration period. In four Phase IIIb trials in painful osteoarthritis or low back pain where tapentadol PR could be supplemented with tapentadol IR up to a total daily dose of 500 mg of tapentadol for up to 12 weeks, similar profile of TEAEs were reported⁽²⁵⁻²⁷⁾. In one of 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⁽²⁸⁾. Respiratory depression with tapentadol occurred rarely and had limited clinical relevance. No clinically relevant changes in vital signs, ECG parameters, or laboratory values were observed⁽¹⁷⁾.

Drug withdrawal as an adverse event was uncommon (below 1%) and classified as mild (KF5503/34). When systematically assessed by the Clinical Opiate Withdrawal Scale, more than 80% of the subjects had no withdrawal. Most cases were classified as mild and some as moderate in those subjects with withdrawal. No case was classified as moderately severe or severe. Accordingly, tapering of therapy is not required, but subjects should be cautioned about the possibility of experiencing withdrawal symptoms.

Tapentadol is not a prodrug and does not have active metabolites⁽⁵⁾, resulting in a profile not likely to be altered by metabolic factors. No clinically relevant changes were observed when combined with the commonly used non-opioid analgesics paracetamol, acetylsalicylic acid, and naproxen in its pharmacokinetic properties⁽²⁹⁾.

To address the potential risk of adverse events in patients receiving tapentadol, Janssen Pharmaceuticals developed and 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⁽⁵⁾. Because morphine was twice as potent as tapentadol in this study, 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⁽¹⁹⁾. 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 drug 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), with nausea, vomiting, and diarrhoea being reported in ~22%, 11%, 6% of the subjects for tapentadol ER and 2/1154 patients reported withdrawal syndrome.

To date, the evidence for development of tolerance to the analgesic effects of tapentadol are low. In the Phase III trials, patients were maintained on tapentadol PR 100 to 250 mg for painful osteoarthritis or low back pain^(24, 30) for 12 weeks followed a 3-week titration to the optimal analgesic dose. The pain relief for tapentadol PR was maintained at a constant level without a relevant increase in dose intake. Similarly, in subjects with painful diabetic peripheral neuropathy, pain relief using fixed doses was maintained over a 12 week period⁽³¹⁾. In subjects treated with either tapentadol PR or oxycodone CR for up to a year, an analysis of mean pain scores and mean total daily doses revealed stability for both parameters, suggesting that there was no development of tolerance to tapentadol PR. The analysis indicated that mean total daily dose increased until approximately 4 weeks and there was only a slight increase in dose by the end of the trial⁽³²⁾.

8. Abuse potential

Tapentadol has been evaluated in standard animal models of abuse liability. 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).

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 cited in Australian Therapeutic Goods Association 2011). 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. Negative subjective-rated effects were observed 2 to 6 h after dosing. 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. In another study examining lower doses of 25, 50, and 75 mg tapentadol IR within the normal therapeutic analgesic dose range, positive subjective ratings on 'Good Effects', 'like the Drug', 'Willing to Take Again', 'Street Value', and no 'Bad Effects' for 75 mg. Low and high doses of tapentadol reduced pupil diameter but no doses impaired the digit symbol substitution test⁽³³⁾. Importantly, the observations that the positive subjective effects for tapentadol had a more rapid onset and offset than for tramadol and hydromorphone with fewer negative subjective effects could be a concern for increased frequency of use of tapentadol.

Other 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. Opioid-naïve subjects first exposed to tapentadol IR are less commonly observed opioid to 'doctor shop', i.e., defined as patients with prescriptions with at least one day of overlap, written by ≥ 2 different prescribers and filled in 3 or more pharmacies, as compared to oxycodone IR⁽³⁴⁾ and 2014. In a retrospective cohort study comparing two claims databases, the risk of opioid abuse for tapentadol IR was 65% less than with oxycodone IR and the risk of receiving an abuse diagnosis with tapentadol was lower than with oxycodone^(35, 36).

Reports on tapentadol from internet websites devoted to sharing information and experiences on drug 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.”

To reduce the potential of tampering with tapentadol extended release tablets, a physical barrier technology (INTACTTM (Grunenthal GmbH, Aachen, Germany) was developed. Only 14% of intranasal prescription opioid abusers allowed to manipulate the tablets reported they would attempt to snort the larger particles and only 18% of intravenous prescription opioid users reported they would attempt to inject the gel-like preparation suggesting the abuse-deterrent formulation was mostly successful⁽³⁷⁾.

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^(21, 38, 39). The rate of discontinuation from tapentadol was lower than oxycodone based on the pooled analysis of three studies in 3000 patients with either osteoarthritis or back pain due to the improved tolerability profile of tapentadol⁽⁴⁰⁾. 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^(22, 41, 42), end-stage degenerative knee or hip joint disease^(19, 20, 43), and hysterectomy (Study KF5503/35). Tapentadol ER provided effective analgesia for patients with chronic osteoarthritis and low back pain^(26, 30, 40, 44, 45) or pain associated with diabetic peripheral neuropathy^(31, 46). Data from three randomized, double-blind phase III studies of similar design in patients with chronic osteoarthritis knee pain found tapentadol ER (100-250 mg bid) to produce pain relief and with better gastrointestinal tolerability than oxycodone CR regardless of baseline pain intensity, prior opioid experience, gender, or body mass index⁽⁴⁷⁾. Similar results were found in Japanese and Korean patients for tapentadol ER in a clinical trial for severe, malignant pain⁽⁴⁸⁾. 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⁽⁴⁹⁻⁵¹⁾. A number of symptoms on the Neuropathic Pain Symptoms Inventory were reduced following tapentadol in patients with chronic low back pain with neuropathic component⁽⁴⁵⁾.

10. Listing on the WHO Model List of Essential Medicines

Tapentadol is not listed in the 18th edition of WHO Model List of Essential Medicines (April 2013).

11. Marketing authorizations (as a medicine)

Grünenthal GmbH, Aachen, is the originator of tapentadol and holds marketing authorizations in European Union countries, Australia, and selected Latin American countries. Tapentadol is marketed under the trade names Palexia[®], Yantil[®], Palexias[®], and Palexis[®]. In the US the product is marketed under the trade name Nucynta[®] by Janssen Pharmaceuticals Inc. Tapentadol was first approved in the US on 20 Nov 2008, the international birth date (IBD). The product is authorized in 37 countries: Australia, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Cyprus, the Czech Republic, Denmark, Ecuador, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Mexico, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, the United Kingdom, and US.

In the US, Nucynta[®] is indicated for the treatment of moderate to severe acute pain in patients 18 years of age or older, for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time, and for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. In the EU it is indicated for the relief of moderate to severe acute pain in adults and for the management of severe chronic pain in adults, which can be adequately managed with opioid analgesics.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

12. Industrial use

None

13. Non-medical use, abuse and dependence

Data on non-medical use, abuse and dependence of tapentadol for the first 24 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⁽⁵²⁾. 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, an analgesic with a less restrictive schedule than tapentadol worldwide, and notably lower than that of oxycodone and hydrocodone, two drugs with similar control levels to tapentadol. 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⁽⁵²⁾.

Non-medical use of prescription opioids was reported by 1,626 of 13,514 US college students (12.0%) and tapentadol IR use was reported by 101 students (0.7%) with majority of these non-medical users of tapentadol IR being multi-drug users. The primary route of tapentadol IR administration was oral (swallowed or chewed), followed by inhalation (smoked or snorted). The rate of non-medical tapentadol IR use per 100,000 population was highest in 4Q2009 (0.013 per 100,000 population) and decreased over the subsequent 2 years to 0.004 per 100,000 population. Similarly, the rate per 1,000 unique recipients of dispensed drug (URDD) was highest in 4Q2009 (0.66 per 1,000 URDD) and decreased to 0.06 per 1,000 URDD⁽⁵³⁾. Taken together to date, the results from the different RADARS System programs (Drug Diversion Rates; Poison Center Network; Opioid Treatment Program; Survey of Key Informants' Patients Program) 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 (which is not scheduled). Despite the increasing availability of tapentadol IR, rates of abuse have remained relatively stable. Overall, tapentadol demonstrates a lower range of events based on the URDD that classical strong opioids.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

As a newer medication, 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 medications. Most hospital formularies have only recently listed tapentadol. Data on the incidences of overdose for tapentadol alone is limited to a single case report of an intravenous overdose with estimates of 1.05 mg/L in femoral blood and 3.2 mg/L in heart blood were reported as a forensic case study in the US⁽⁵⁴⁾. Otherwise, only a few reports of overdose death from multiple drug use including tapentadol have been reported (Coroner's Report, California and Alabama, US <http://www.cal-tox.org/resourcefiles/Tapentadol%20CAT.pdf>). In addition, a report of tapentadol has not been included directly in the questionnaires for the Monitoring the Future Survey 2012 or appeared in SAMHSA's 2012 National Survey on Drug Use and Health, California Poison Control System, or Community Epidemiology Work Group 2013. From the Drug Abuse Warning Network 2011, there were no emergency department visits due to tapentadol. Therefore, at the current time, the magnitude of public health problems related to misuse, abuse and dependence is minimal.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

Janssen Research and Development has expanded its licensing agreement with the Grunenthal Group to register, manufacture and commercialize Tapentadol in additional regions, including selected Asia Pacific, Latin American, African, and New European

countries including Turkey and Greece, under Grunenthal's Nucynta /Palexia /Palexis trademark for both the immediate and prolonged-release, or IR and PR, formulations.

Under the terms of this expanded agreement, Janssen has the right to market Nucynta /Palexia /Palexis in more than 80 additional countries. Janssen and Grunenthal will each manufacture the IR and PR/extended release formulation for certain regions. Janssen will be responsible for marketing, distributing, promoting and selling the product in the entire licensed territory.

The Grünenthal Group in its licensing agreement with Janssen Research and Development 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.

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; 2011 - 403,000 g; 2012 – 5,400,000 g; 2013 - 13,750,000 g. The established quotas for 2014 are 17,500,000 g suggesting an increased demand in the past years. The increase in volume needs to be evaluated in light of ongoing launch activities. These estimated do not include tapentadol that will be imported from other countries to the US.

There are currently at least 32 commercial sources for tapentadol from regions around the globe. Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

No information or evidence available for illicit manufacture or trafficking. However, the lack of tapentadol precursors and the complex chemical synthesis process would make the illicit synthesis of tapentadol problematic and unlikely to occur.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

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. On November 20, 2008, the Food and Drug Administration (FDA) approved tapentadol for marketing in the United States as a prescription drug product for the treatment of moderate-to-severe acute pain. The Assistant Secretary for Health, Department of Health and Human Services (DHHS)

sent the Deputy Administrator of DEA a scientific and medical evaluation and a letter recommending that tapentadol be placed into schedule II of the CSA. Enclosed with the November 13, 2008, letter was a document prepared by the Food and Drug Administration (FDA) entitled, “Basis for the Recommendation for Control of Tapentadol in Schedule II of the Controlled Substances Act.” US Department of Justice, Drug Enforcement Administration, 21 CFR Part 1308 placed tapentadol into Controlled Substances Schedule II on June 22, 2009.

Based on the Australian Public Assessment Report in 2011 by the Australian Therapeutic Goods Administration 2011, tapentadol was scheduled as S8 as a Controlled Drug..

Approved by Health Canada in December 2010, tapentadol has been available for use in Canada since March 2011 and is now included on the Triplicate Prescription Program (TPP) Medication List. Due to its potential for psychological and physical dependence, Health Canada has included tapentadol as a Schedule 1 drug under the Controlled Substances Act.

The United Kingdom via The Misuse of Drugs Act 1971 (Amendment) Order 2011 classified tapentadol as a controlled drug under Schedule 2 to the Misuse of Drugs Act 1971 and subjects tapentadol to control as Class A and C drugs respectively under Parts I and III of that Schedule.

In March 2012, New Zealand classified tapentadol under the Misuse of Drugs Act 1975.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

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

Additive central nervous system effects between the concomitant use of tapentadol and other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol and illicit drugs) have not been systematically studied. Although there is little data from the current clinical data, interactive effects could occur due to the pharmacological class of tapentadol, potentially resulting in respiratory depression, hypotension, profound sedation, serotonin syndrome, or coma. In the Phase II/III multiple-dose double-blind studies, 182 of 2694 subjects (6.7%) treated with tapentadol IR concomitantly took selective serotonergic reuptake inhibitors (SSRI) or serotonin-noradrenaline reuptake inhibitors, which could potentially interact with the mechanism of action of tapentadol. The safety profile of subjects taking concomitant serotonergic reuptake inhibitors or serotonin noradrenaline reuptake inhibitors appeared to be similar to subjects who were not taking one of these medications.

Due to the recent development of the tamper-resistant coatings^(55, 56), tapentadol will be limited to forms which cannot be easily injected and therefore the adverse physical health consequences may be limited.

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Annex 1:**Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of Tapentadol**

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 68 Member States answered the questionnaire for tapentadol. Of these, only 29 respondents (AMR 6, EUR 19, SEAR 1, WPR 3) had information on this substance.

LEGITIMATE USE

Twenty-five respondents stated that tapentadol was currently authorized or in the process of being authorized/registered as a medical product in their country; these are from three WHO regions - 18 EUR, five AMR and two WPR. The earliest authorization reported is 2008 and is used in the treatment of moderate to severe pain, both acute and chronic.

The different formulations reported are presented in the table below.

| | Strength |
|---------------------------|----------------------------------------------|
| Tablet | 25mg; 50mg; 75mg; 100mg; 150mg; 200mg; 250mg |
| Prolonged release tablets | 25mg; 50mg; 75mg; 100mg; 150mg; 200mg; 250mg |
| Oral solution | 4 mg/ml; 20 mg/ml |

Brand names mentioned by the different respondents are included in table below.

| Name | Number of mentions |
|---------------------------------------------------------------------------------------------------------------|---------------------------|
| Palexia | 16 |
| Palexia retard | 8 |
| Palexia Depot | 3 |
| Palexis | 2 |
| Palexia SR | 2 |
| Yantil | 2 |
| Palexias, Nucynta, Nucynta ER, Yantil retard, Tapentadol Grünenthal, Tapentadol Grünenthal retard, Palexia IR | 1 each |

Six responded that tapentadol was used in medical or scientific research. For legitimate use, 21 respondents stated that they imported tapentadol and 3 manufactured it. Estimated quantities of use reported varied from 5 kg to 2000 kg. Several countries did not report this data.

HARMFUL USE

While three respondents confirmed recreational/harmful use, thirteen stated there was no such use. Three respondents stated the common routes of administration as oral. The substance was obtained for such use by diversion in two responses and by trafficking in one. Common formulations available were reported as tablet by three and powder by one. It is used by the general population as stated by two respondents. One respondent reported 1,935 emergency

room visits for 2011 (equal to 0.6 visits per 100, 000 population of the reporting country). Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by tapentadol. These included a report of 10 cases of withdrawal and 46 cases of tolerance, including two cases were both occurred, in 2012. The adverse effects reported are similar to other opioid analgesics and include a number of CNS and gastrointestinal effects.

CONTROL

Of those providing information on this substance, 27 reported that tapentadol was controlled under legislation that was intended to regulate its availability; 24 under “controlled substance act”, 2 under “medicines law” and 1 under “other” laws. Only three respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving tapentadol, 1 reported trafficking and 2 reported diversion.

Details on seizures are presented below.

| | 2011 (number of respondents) | 2012 (number of respondents) |
|---------------------------|-----------------------------------------------|-----------------------------------------------|
| Total number of seizures* | 131 (1) | 163 (1) |

* An additional 3 respondents reported zero seizures in 2011 and 2012

IMPACT OF SCHEDULING

Twenty-three respondents reported that if Tapentadol was placed under international control, they would have the laboratory capacity to identify the substance. One respondent indicated that the availability for medical use would be affected if internationally controlled.