Decentralised Procedure

Public Assessment Report

Palexia 50 mg, 75 mg, 100 mg film-coated tablets

Yantil 50 mg, 75 mg, 100 mg film-coated tablets
Tapentadol

DE/H/2020-2021/001-003/DC

Applicant: Grünenthal GmbH

| Reference Member State | DE |
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<td>N 02 AX 06</td>
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<td>50/ 75/ 100 mg Film-coated tablet (Immediate Release, IR)</td>
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<td>Grüenthal GmbH&lt;br&gt;Zieglerstr. 6,&lt;br&gt;52078 Aachen, Germany</td>
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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Palexia/Ixarto (Yantil) 50, 75, 100 mg film-coated tablets, in the treatment of moderate to severe acute pain, which can be adequately managed only with opioid analgesics is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The present Marketing Authorisation Application (MAA) for Palexia and Ixarto (new name Yantil) concerns three strengths of the immediate-release formulation (50 mg, 75 mg and 100 mg film-coated tablets) of the novel drug substance tapentadol hydrochloride.

Tapentadol hydrochloride is a new chemical entity (NCE) and was developed by Grünenthal, Aachen, Germany. It combines µ-opioid receptor agonist activity with noradrenaline (NA) reuptake inhibition in one molecule. The correspondent ATC code to tapentadol is N02 AX 06. Clinical development was performed in cooperation with Johnson & Johnson Pharmaceutical Research and Development L.L.C.

The 50, 75 and 100 mg film-coated tablets have been authorized by the US FDA in November 2008. In Europe, the MAA was submitted via the Decentralised Procedure according to Art. 28(3) of Dir. 2001/83/EC with Germany acting as the reference member state (RMS) and all other members of the European Community being involved as CMS (DE/H/2020-21/01-03/DC). Concerning a new chemical entity, the Palexia/Ixarto dossier is submitted as a full, stand-alone application according to Art. 8(3) of Dir. 2001/83/EC.

In parallel with the present IR 50 mg, 75 mg and 100 mg film-coated tablets, MAAs have also been submitted for five strengths of a prolonged release formulation of tapentadol (Palexia / Ixarto SR 50/100/150/200/250 mg prolonged release tablets). The dossier of the prolonged release formulations (DE/H/2020-21/04-08/DC) will be assessed in a separate clinical AR and separate quality AR for the product part.

II.2 About the product

Tapentadol is a novel centrally active anti-nociceptive agent proposed to be used for the treatment of severe acute pain. It has distinct properties with an apparent dual mode of action, being both a mu-opioid receptor agonist and an inhibitor of norepinephrine (re)uptake thus differing from pure mu-opioid receptor agonists. Both mechanisms are likely to contribute to the analgesic effects of the compound.

The concept of developing analgesics with a dual mode of action (µ-receptor agonism and norepinephrine uptake inhibition) is not entirely new. An analogue mechanism of action has been established for tramadol. The clinical use of tramadol is widespread in Europe. The originator product of tramadol (Tramal, MAH: Grünenthal GmbH) that is available in different dosage forms (mainly IR oral liquid and prolonged release tablets) is licensed in Germany (DE/H/108 and DE/H/136) for the treatment of moderate to severe acute and chronic pain. The chemical structure of the NCE tapentadol bears significant similarities with tramadol, which has also been developed by Grünenthal.

The hydroxyphenyl substituent ensures that tapentadol is not a prodrug (not requiring metabolism prior to becoming active). Additionally tapentadol is a pure enantiomer but not a racemic mixture.
II.3 General comments on the submitted dossier

Formal Scientific Advice on the clinical development of tapentadol IR was given by the CHMP to Gruenenthal in July 2006 (EMEA/CHMP/SA WP/266045/2006). Furthermore, in 2008 a total of eight pre-submission meetings were held at various National Authorities across Europe (CZ, NL, DE, UK, SE, IT, FR, ES).

To date, more than 4000 subjects have received tapentadol IR in Phase 1, Phase 2, and Phase 3 clinical studies. Several Phase 2 double-blind, placebo or active controlled studies were designed to provide guidance for the development of the pivotal clinical Phase 3 studies, including single-dose studies of acute pain following third molar tooth surgery (extraction) or bunionectomy, and 2 multiple-dose studies following bunionectomy.

Overall, five phase III studies have been conducted to give proof of the efficacy and safety of tapentadol IR for the proposed general indication (including visceral and somatic pain states), i.e. the relief of severe acute pain with 50 mg, 75 mg, and 100 mg doses given every 4 hours to 6 hours as needed.

The pain models that were examined are standard to demonstrate efficacy in acute pain. They cover both visceral components (post-operative pain after hysterectomy) and typical somatic pain states (post-operative pain after bunionectomy, hip replacement) and are therefore considered to be in line with the provisions of the CHMP nociceptive pain guideline CHMP/EWP/612/00. The primary efficacy endpoints cover short-term pain treatment (SPID24-hours in hip replacement, SPID48-hours in bunionectomy) and longer-term periods (SPID5-day in end-stage degenerative joint disease).

The overall clinical concept and the quality of data presentation in the clinical dossier are considered to be adequate.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For all studies presented within this AR, the applicant declares that the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

GCP inspections have been conducted in single sites involved in the phase III study KF5503/35 in patients with post-operative pain after hysterectomy. Subsequent to GCP findings some of the participating sites were excluded from the dataset. At Day 106 the Applicant provided an Addendum to the clinical trial report of study KF5503/35 based on the reduced dataset. The data that were presented in this Addendum are considered valid.

Relevant toxicological investigations were conducted in compliance with GLP standards. However, not all safety pharmacology studies are conforming to GLP regulations, because they were performed before ICH S7A and S7B came into force. Nonetheless, these studies are satisfactorily documented.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects
Drug substance

Tapentadol hydrochloride is a new chemical entity, not described in any pharmacopoeia. The content of this ASMF follows the requirements of the note for guidance “Chemistry of New Active Substance” (CPMP/QWP/130/96 Rev1). Letter of access has been provided. Tapentadol hydrochloride drug substance is manufactured through a series of organic synthesis steps starting from commercially available chemicals. No major concerns raised during the assessment of the documentation regarding the ASMF provided. The questions regarding the open part and restricted part have been sufficiently answered. The re-test period of 36 months is acceptable.

Drug Product

The finished product is presented as film-coated tablet. The excipients used in the products are conventional pharmaceutical ingredients. The function of each ingredient included in the product has been described. Levels of excipients have been selected on the basis of optimisation studies. Preliminary compatibility studies were performed using potentially useful excipients for the intended formulations. Dissolution profiles have been presented.

The finished product specifications are in compliance with the general pharmacopoeial requirements and the batch data submitted, and are controlled with valid methods. Stability studies undertaken justify a maximum shelf life of 36 months (without label claim).

III.2 Nonclinical aspects

Pharmacology

Tapentadol is an effective agonist of µ-opioid receptors, which also displays non-opioid action by inhibition of noradrenaline re-uptake. The affinity of tapentadol to µ-receptors of rats and humans is about 15- or 20-fold higher than that of the structurally-related substance tramadol. In contrast, the purified active (+)-M1 metabolite of tramadol, binds with 2.7-fold higher affinity to the human µ-receptor than tapentadol. The ratios of the rat brain/CNS concentrations of tapentadol to the µ-receptor affinity (3) and to the noradrenaline re-uptake inhibition (1) are higher than the respective ratios of the tramadol metabolite M1 for µ-receptor affinity (0.7) and of the tramadol (-)-enantiomer for noradrenaline re-uptake inhibition (0.5). The distinctly different brain/CNS concentration to activity ratios for tapentadol and tramadol make it conceivable that the synergistic effect of both mechanisms of action is different for the two molecules. Tapentadol demonstrated its analgesic efficacy in various animal models of acute, neuropathic and inflammatory pain. These studies also delineated the actions of tapentadol on µ-opioid receptor and noradrenaline re-uptake. Moreover, absence of an inhibitory potential on serotonin re-uptake was shown. In these pain models, tapentadol was clearly more potent than tramadol but less effective than morphine when given by the intravenous or intrathecal route. Onset of analgesia was rapid and of short duration. The higher in vivo potency of tapentadol compared to tramadol seen after parenteral administration was lost following oral administration consequent to the extensive first-pass metabolism.

Secondary pharmacodynamic effects of tapentadol are typical for the class of µ-opioid receptor agonists and comprise emetic effects in ferrets at high doses. However, tapentadol exerted a marked anti-emetic activity against morphine-induced emesis, but was only moderate efficacious when emesis was evoked by cisplatin. These results indicates that emesis can be induced by µ-opioid receptor stimulation and that the emetic potential of tapentadol is weaker compared to morphine. Tapentadol showed also antitussive effects in rats with ED₅₀ of 0.9 mg/kg i.v., which was 7-fold higher than that of the reference drug codeine phosphate (ED₅₀ = 6.7 mg/kg i.v.).

The safety pharmacology of tapentadol was studied in various in vitro studies and in mice, rats, guinea pigs, dogs and rabbits in vivo focussing on potential undesirable effects on physiological functions of
cardiovascular, respiratory and central nervous system. Supplemental safety pharmacology studies on
effects of tapentadol on gastrointestinal and renal functions were additionally performed. Albeit, not
all of these studies were conducted in compliance with current GLP requirements, they are all
appropriately documented. In these investigations, tapentadol showed effects typical for a µ-opioid
receptor agonist, including depression of respiratory and central nervous system functions as well as
gastrointestinal inhibition. Nonetheless, tapentadol showed generally a lower potential for these side
effects than morphine indicating a better clinical safety profile.
Tapentadol demonstrated very mild CNS depressant activity and impaired motor coordination only at
an extremely high dose in the barbiturate-induced sleep model in mice. In addition, tapentadol affected
the autonomic nervous system, increased muscle tone and revealed proconvulsant action starting in the
upper anti-nociceptive dose range. A direct convulsant effect, however, was induced only at high i.v.
doses exceeding anti-nociceptive levels.
High i.v. doses of tapentadol transiently increased heart rate and arterial blood pressure in conscious
rats and dogs, whereas blood pressure was lowered in anaesthetised rabbits and dogs. Tapentadol did
not unveil a risk for QT interval prolongation and associated cardiac arrhythmias in several non-
clinical in vitro and in vivo investigations, except a delay in cardiac repolarisation observed at
extremely high doses in vitro. This is in agreement with absence of an arrhythmogenic potential in a
thorough QT study in humans, so the risk for treatment-related ventricular tachycardia of the
“Torsade de Pointes”-type or other potentially fatal ventricular arrhythmias in patients is considered to
be low.
There were no clinically relevant effects of tapentadol on the renal / urinary system, nor effects on
muscle relaxation. A competitive antagonistic effect against acetylcholine was noted, but was 300-fold
lower than that of atropine.

Pharmacokinetics
The pharmacokinetic properties of tapentadol were investigated in various species including mice,
rats, rabbits, dogs and monkeys. When parenteral routes of administration were tested, linear
pharmacokinetic characteristics without accumulation and no gross differences between sexes were
observed in all species. Absorption of tapentadol was rapid after oral administration, but oral
bioavailability was substantially lower in animals compared to man consequent to an extensive first-
pass effect. Higher bioavailability in a similar range as observed for humans was initially only found
in mice after single dosing. However, this could not be confirmed in subsequent toxicokinetic
evaluations. Consequently, animals were exposed to relatively low tapentadol levels in toxicity studies
when the drug was orally administered, which rendered other routes necessary to achieve higher
exposure levels. These findings also explain the reduced efficacy of orally administered tapentadol in
pharmacological in vivo studies described above.

Following absorption, tapentadol widely distributes throughout the body. The binding to plasma
proteins is relatively low, whereas reversible interaction with melanin was apparent. Effective
penetration across the blood/brain and placental barriers and secretion into milk was additionally
evident. Potential effects on the breast-fed infant were satisfactorily considered for SPC and PL,
because mothers are advised not to use the drug during breast-feeding.

Tapentadol is predominantly metabolised to the main inactive metabolite tapentadol-O-glucuronide in
all species investigated. UGT1A6, 1A9 and 2B7 were identified as major UDP-glucuronyl transferase
isoforms which are able to generate tapentadol-O-glucuronide. In contrast, oxidative reactions
contribute to a minor extent to the biotransformation of tapentadol. In man, hydroxylation (CYP2D6,
CYP2B6 and CYP2C19) of the aromatic ring system with subsequent conjugation, and
N-demethylation (CYP2C9, CYP2C19 and CYP2C8) followed by conjugation were detected.

Almost complete and rapid excretion of tapentadol metabolites via urine was found in all species
including man. These findings support the high absorption and metabolic rate determined in other
investigations. Thus, no pronounced accumulation was observed after repetitive dosing. Effects of
renal insufficiency on the pharmacokinetics of tapentadol have been clinically evaluated.
Toxicology
In most toxicity studies, animals were exposed to lower amounts of tapentadol compared to maximum human levels obtained with immediate or prolonged-release formulations. Apparently, the pharmacological characteristics of tapentadol prevented higher exposure of study animals and hence calculation of notable safety margins.

The acute toxicity of tapentadol was analysed in mice and rats after oral (gavage) and i.v. routes. Deaths occurred within 15 min (i.v.) or up to several hours (p.o.) and were probably related to depression due to exaggerated pharmacological effects. Clinical signs included increased sensitivity to touch and noise, irritability, and escape response as well as irregular respiration, and convulsions. Mode of death and clinical signs are characteristic for an acute opioid overdose.

In two repeated-dose toxicity studies with tapentadol in mice over 13 weeks comparing dietary with gavage administration, main target organs for toxicity were CNS and liver. Hepatic changes included dose-related hepatic and hepatocellular hypertrophy and necrosis, which may be regarded as an adaptive response of the liver due to extensive metabolism of tapentadol.

Repeat-dose toxicity studies in rats were conducted with s.c., i.v. and oral (gavage and diet) route of administration for 7, 10 and 14 days and 1, 3 (two studies) and 6 months. Overall, results confirmed the target organ toxicity in CNS and liver that had been observed in mice. Dose-dependent effects on the CNS were generally observed in all rat studies and resulted in deaths by respiratory depression and further clinical symptoms such as fearfulness, excited behaviour, recumbency, hunched posture, sedation and laboured respiration. These signs of CNS toxicity were reversible in surviving animals. Hepatic findings included elevated enzyme levels (ALAT, ASAT, gamma-GT), dose-related hepatic hypertrophy and increased incidences of hepatocellular hypertrophy. As seen in mice, these effects can be regarded as an adaptive response without clinical relevance. Activation of Kupffer cells and hepatocellular necrosis or fibrosis was not observed. All of these findings in the liver were completely reversible. Liver toxicity was not observed in dogs and monkeys. In clinical trials, the majority of subjects had normal liver parameters, whereas abnormal laboratory values were comparable between placebo and verum groups. Hence, hepatic findings found in rodents (rat and mice) do not raise concerns for humans.

Repeat-dose toxicity studies with tapentadol in dogs were conducted by the s.c., i.v. and oral (gavage) route for 2, 4, 14 and 52 weeks. In accordance with observations in rodents, target organs of toxicity were mainly the CNS, respiratory, cardiovascular and gastrointestinal system. Moreover, local toxicity following s.c. and i.v. administration was observed such as haemorrhages, reversibly dark red discoloured injection sites, acute/subacute inflammatory infiltrates, fibrosis, phlebitis and thrombophlebitis. Since tapentadol will be orally administered to human patients, the local findings after s.c. and i.v. administration are not considered clinically relevant. Dose-dependent CNS toxicity comprised convulsions, salivation, restlessness, laboured breathing, rhinorrhea, decreased activity and tachypnea. Severities of clinical signs decreased with increasing study duration and were reversible in surviving animals.

In dogs, non-persistent dose-dependent prolongations of QTc time were measured, which were more pronounced at the beginning of the studies. The QTc effects are in contrast to the results of cardiohaemodynamic studies in anaesthetised rabbits and in anaesthetized or conscious dogs. Moreover, they are also contrary to the outcome of a thorough QT study with the IR formulation of tapentadol. Thus, the QTc effects observed in dogs are considered to be without clinical relevance.

As expected for an opioid agonist, tapentadol-related gastrointestinal toxicity was detected in dogs. In the 14 day study with p.o. administration, activation of the enteric lymphatic system (Peyer’s patches) in the small and large intestine with activated lymphoid follicles was apparent, but was regarded as a normal biological reaction to an exogenic stimulus. As no corresponding findings were observed in subsequent long-term studies, this finding is unlikely to be of clinical relevance.

Tapentadol has been evaluated in a standard battery of genotoxicity tests. No evidence for a mutagenic potential of tapentadol was found in bacteria. However, tapentadol was clastogenic following metabolic activation in the first of the two chromosome aberration assays in vitro. This could not be
reproduced by the contract laboratory in another test using the same assay and were also not confirmed in two *in vivo* studies.

Long-term carcinogenic potential of tapentadol was studied over two years in two rodent species. In mice, the incidences of liver hepatocellular tumours in males were rated to be without importance in agreement with a pertinent FDA draft guideline (CDER. Guidance for industry. Statistical aspects of the design, analysis and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals, May 2001). Apparently, the decision to rate this incidence as either positive or negative depends on the underlying statistical calculation (levels of significance). From a toxicological point of view, it should be stated that hepatocellular tumors are common in mice and there were no further neoplastic or non-neoplastic findings in this species. Additionally, this finding was not confirmed in the second carcinogenicity study in rats and the liver is not a target organ for toxicity in humans. On the other hand, there are no relevant safety margins and equivocal findings were reported from an *in vitro* genotoxicity study. As it is practically impossible to detect genotoxic or carcinogenic effects of new drug substances on a clinical basis, there is a remaining risk for a carcinogenic potential at high doses of tapentadol in humans. Thus, the results of this study should be clearly described in the SPC. Results of the carcinogenicity study in rats indicate that there may be a weak tendency to a higher incidence of hepatocellular adenomas and hepatocellular carcinomas in rats; however these observations were not statistically significant. Non-neoplastic findings comprised hepatocellular hypertrophy, which was rated as an adaptive response to the repeated exposure to high doses of tapentadol. Moreover, follicular cell hypertrophy and focal follicular cell hyperplasia in the thyroid gland were observed in high dose females, which were considered as secondary to the liver cell hypertrophy and the resulting enhanced liver enzyme activities.

Tapentadol did not affect male and female fertility in rats when given by the i.v. route, but resulted in systemic toxicity in both genders, which impacted on pre- and postimplantation losses. In studies of embryo-fetal development in rats, ptyalism was the only observation after gavage administration of up to 200 mg/kg b.i.d., whereas following i.v. dosing, maternal toxicity such as convulsions, decreased respiratory rate and foetal numbers was prominent. In rabbits, tremor, accelerated respiratory rate and increased post-implantation losses and number of dead foetuses were additionally observed. Subcutaneous administration of tapentadol reduced body weights of rats and rabbits, promoted prone position, increased foetal mortality and resulted in skeletal variations. Moreover, miosis in rabbits and local intolerabilities in terms of eschar formation and haemorrhagic foci were noted in rats. Consistent with these findings, body weight gain was reduced in a pre- and postnatal development study in rats, while mortality was elevated in the F1 generation. Most notably, tapentadol did not unveil any teratogenic potential even at maternotoxic dosages.

Tapentadol has the potential to induce physical and psychological dependence with potency between those of morphine and tramadol. Typical withdrawal symptoms following abrupt cessation of treatment were also observed in clinical trials (see clinical report). Thus, tapentadol should be classified as a substance with a relevant drug abuse potential and its availability adequately restricted by local regulations.

With regard to the environmental risk of tapentadol, potential influences on aquatic organisms and the terrestrial compartment were appropriately evaluated. There will be no risk for sediment dwelling organisms and tapentadol does not show a potential for bioaccumulation.

### III.3 Clinical aspects

**Pharmacokinetics**

The absorption of tapentadol following an IR dose is both fast, given the median tmax of around 1.25 hours and almost complete, based upon the 14C-tapentadol study HP5503/05. The absolute oral bioavailability of tapentadol under fasting condition was 32.0% (95% CI: 29.4% to 34.8%). Together, these results indicate that tapentadol undergoes extensive first-pass metabolism. Indeed, 96% of an administered dose of tapentadol is eliminated via urine as tapentadol metabolites. Glucuronidation was the major metabolic pathway in all animal species investigated in non-clinical studies as well as in
humans (HP5503/05). The most prominent metabolite detected in serum was tapentadol-O-glucuronide (80% to 85% of the conjugates).

The effect of food on the bioavailability of tapentadol was assessed in 2 studies. Study HP5503/34 is considered the key trial evaluating the effect of a high-fat, high-calorie breakfast eaten within the 30 minutes before tapentadol administration, on the bioavailability at the highest recommended dose of 100 mg tapentadol. The Cmax and AUC of tapentadol administered as a 100 mg IR tablet after a high-fat, high-calorie breakfast increased 16% and 25%, respectively, compared to fasted administration. The Tmax was prolonged by about 1.5 hours with a median Tmax of 3 hours (range 1-6 h) in the fed state and 1.5 hours (range 1-4 h) in the fasted state. The applicant did not restrict the use of tapentadol with respect to meal consumption. The PK data obtained in the fed state are appropriately reflected in the SmPC with regard to doubling of Tmax. Based upon the efficacy data obtained during phase II/III trials, this food effect does not appear to be of clinical relevance.

Dose-proportionality of the pharmacokinetics of tapentadol was investigated in several single studies (HP5503/03, HP5503/07, HP5503/09, HP5503/13, partly as marginal study objective) and in a cross-study comparison. Fifteen Phase 1 studies, covering a dose range from 21.5 mg to 200 mg were included in this cross-study comparison. In dose-linearity study HP5503/13 the median time to serum Cmax for tapentadol was 1.5 to 2.0 hours and approximate dose proportional increases in blood levels for up to 150 mg could be demonstrated. However, considering the entire phase I clinical programme, dose proportionality for Cmax and AUC could not be shown in the cross-study comparison.

In a single and multiple dose study covering a dose range of 75 to 175 mg (HP5503/13) steady state was reached within the first 24 hours after 3-4 drug administrations. Two Phase 1 multiple-dose studies were performed in healthy subjects, one was a dose escalating study (HP5503/13) and one was to evaluate ECG parameters upon tapentadol IR dosing (HP5503/25). The calculated accumulation ratio (ratio of AUC [multiple dose] and AUC0-6h [single-dose]) was between 1.4 and 1.7 in study HP5503/13. The accumulation ratio of tapentadol-O-glucuronide was in the range of 1.7 to 2.0 (HP5503/13). The accumulation ratio for tapentadol is close the theoretical ratio derived from equation: \( R = \frac{1}{1-\frac{\lambda}{\tau}} \). With a dosing scheme of every 6 hours, the predicted accumulation ratio amounts to 1.6 (t1/2: 4.3 hours and \( \tau \): 6 hours), suggesting that the accumulation of tapentadol is predictable from single-dose data.

Due to the great number of phase I studies during which PK data were generated the database of the single dose cross-study comparison is large with about 600 subjects. Time to maximum plasma concentration was shown to occur after 1-1.5 hours. With regard to Cmax and AUC∞ inter-subject variability was considerable with 39 and 34%, respectively. This may be explained by the broad database including various populations (healthy subjects, young –elderly etc.), as well as by the considerable time period (approximately 10 years) over which the trials were conducted and the number of centres in both Europe and US that were involved.

**Pharmacodynamics**

Assessment of the pharmacodynamic effects of tapentadol on orocecal transit time (HP5503/09), drug liking (HP5503/14), experimental pain models (HP5503/50, not presented in the AR), and QT/QTc interval (HP5503/25) were included in one study each. Overall, the expected pharmacodynamic profile of a substance with opioid \( \mu \)-receptor agonist activity was confirmed.

Decreases in the initial pupil diameter were dose-dependent (HP5503/03, HP5503/13, and HP5503/04) with a larger and more rapid onset of effect after intravenous than oral administration, reflecting the pharmacokinetic profile.

A high level of convergence and consistency in their drug liking potential was found for tapentadol IR and hydromorphone IR within the different measures of subjective effects in opioid-experienced non-dependent subjects (recreational drug users). In case of a positive approval decision tapentadol would
be classified as controlled drug in Germany.

**Clinical efficacy**

Efficacy of tapentadol IR was shown in all five phase III confirmatory studies encompassing several different pain models, including a visceral pain model, for all doses employed in the studies, i.e., 50 mg, 75 mg, and 100 mg, respectively, taken every 4 hours to 6 hours. These studies examined subjects with moderate to severe pain (moderate was defined as ≥ 4 to < 6 [≥ 4.5 to < 6 in KF5503/33], and severe was defined as ≥ 6 on an 11-point NRS) following abdominal hysterectomy, following bunionectomy, following hip replacement (all 3 days of treatment), or due to end-stage degenerative joint disease (10 days of treatment in an out-patient population).

The dosing interval was at the discretion of the subjects within the 4-6 hour interval time frame. Typically, patients chose to administer a mean of about five doses on the first day of the observation period and about four doses on the second and the third day (KF5503/35, KF5503/32, KF5503/37). Additionally, patients were given the option to administer an "early second dose", i.e. to take the second dose earlier than four hours after the first dose. Various portions of subjects made use of this option with about 20% in KF5503/35 (post-OP pain after hysterectomy), 7-9% in KF5503/32 (bunionectomy), and only 2% in KF5503/37 (bunionectomy).

Although all tapentadol arms demonstrated superiority over placebo in terms of the primary efficacy endpoint (SPID24, SPID48; SPID5-day in end-stage degenerative joint disease), there was no clear dose response relationship across the three tapentadol doses. Only slight numerical trends were observed in study KF5503/35 in post-operative pain after hysterectomy, an inverse dose response was observed in study KF5503/31 in post-operative pain after hip replacement and no dose response relationship was found in study KF5503/33 in pain due to end-stage degenerative joint disease. It is to be considered that the studies were not designed to generate discriminative dose response data. Due to flexible dosing intervals partly overlapping total daily doses were administered across the three tapentadol dose arms (50, 75, 100 mg). After conducting an ANCOVA analysis taking different baseline pain scores (moderate vs severe) into account, a more pronounced numerical dose response (in terms of LS mean difference of SPID24 from placebo) was discernable.

All phase III studies included a placebo- and an active comparator arm (oxycodone 10-15 mg, morphine 20-30 mg). The primary efficacy endpoint was to show superiority of tapentadol over placebo which was consistently achieved. Comparison of responder rates (≥ 30% and ≥ 50% improvement of baseline pain) and analysis of rescue usage yielded mostly plausible and consistent results with the primary endpoint. Both patients with moderate and severe baseline pain were included in the phase III trials. The active comparator arm was announced to be included to validate assay sensitivity.

In early phase II trials in post-operative pain after bunionectomy (KF5503/05) or after third molar dental surgery (KF5503/04) an additional ibuprofen 400 mg dose group was included. In both clinical settings post-surgery pain involves a considerable inflammatory component. This might explain that ibuprofen demonstrated largely higher efficacy than tapentadol 100 mg and about equal or higher efficacy than the tapentadol 200 mg dose group in terms of the TOTPAR8 efficacy endpoint.

Furthermore, the missing dose-response relationship impairs calculation of an approximate dose equivalence ratio between tapentadol and the active comparators (oxycodone, morphine). In study KF5503/37 only one tapentadol IR dose (75 mg) was examined (also included: placebo- and morphine 30 mg arm). At the earlier pain assessment time points (6 and 12 hours) tapentadol 75 mg and morphine 30 mg show similar SPID values, whereas in the further course of the observation period (24, 48 and 72 hours) an increasing difference between both arms in favour of morphine 30 mg is observed. In earlier phase II studies an approximate dose equivalence ratio between tapentadol and morphine of 2.5 to 1 was assumed. Based on the phase III efficacy results of study KF5503/37, this assumption could clearly not be confirmed since morphine IR 30 mg was more than twice as effective as tapentadol IR 75 mg in terms of the primary endpoint (SPID48). It has to be acknowledged, however, that study KF5503/37 was not powered for formal statistical comparison of the tapentadol IR...
and the morphine IR arm. Hence, no conversion ratio of equianalgesic doses between tapentadol and already approved opioid substances (with morphine being the standard reference) can be presented in the SPC. In any way, usual treatment initiation with tapentadol is recommended with the lowest dose. The dose may be increased by administering a higher dose or by shortening the dose interval within the 4-6 hour timeframe.

Clinical safety
The Safety Analysis Set for tapentadol IR is broad encompassing n=2744 subjects in phase II/III multiple-dose double-blind periods, n=870 in phase II single dose periods, n=32 in multiple dose phase I periods, and n=439 subjects in phase I single dose periods. In most studies post-operative pain treatment was examined after various surgical procedures (third molar dental surgery in phase II, hysterectomy, hip replacement, bunionectomy). The phase II/III multiple-dose double-blind periods mostly cover short observation periods (e.g. 48 hours in bunionectomy). A clinical study not related to surgery was also included in outpatients with end-stage degenerative joint disease covering an observation period of ten days. Additionally, a 90-day double-blind (tapentadol IR vs oxycodone IR) safety study (KF5503/34) was conducted giving the patients the option of administering flexible doses (50-100 mg tapentadol IR every 4-6 hours). Across all phase II/III multiple-dose double-blind periods the mean treatment duration was similar between tapentadol IR (18.6 days, mean daily dose 282 mg) and oxycodone IR (17.8 days, mean daily dose 40.2 mg).

The treatment emergent adverse events observed with tapentadol IR treatment, in the dose range of 50 mg to 100 mg given 4 hourly to 6 hourly, are qualitatively similar to those of a centrally acting analgesic. Accordingly, the most common treatment emergent adverse events were those listed in the SOCs gastrointestinal and nervous system disorders, and included nausea, dizziness, vomiting, somnolence, and headache. Most treatment emergent adverse events reported with tapentadol IR were of mild or moderate intensity. The prevalence of the most common treatment emergent adverse events decreased with time.

Apart from symptoms associated with withdrawal, mostly classified as mild, prolonged use (treatment for up to 90 days) was not associated with a change in the safety profile of tapentadol IR. With regard to the incidence of gastrointestinal treatment emergent adverse events tapentadol IR appears to compare favourably with oxycodone IR which was used as the active comparator in studies involving more than two thirds of the subjects in the clinical Phase 3 programme. However, gastrointestinal and nervous system disorders were shown to increase with dose. In evaluating a “substance liability” to induce these kinds of AE by comparing tapentadol and oxycodone, the mean daily doses on which the comparison is based has to be borne in mind.

With prolonged use, the lower reporting rate of constipation for tapentadol IR in comparison to oxycodone IR remained at the same level. These findings may be consistent with the concept of tapentadol’s combined mode of action where there is a reduced µ-opioid receptor agonist activity resulting in fewer gastrointestinal adverse events.

For both laboratory parameters and vital signs (including pulse oxymetry), the few potentially clinically relevant abnormal values did not reveal a consistent pattern of treatment-related change. Reporting rates of individual adverse events in young and elderly subjects were similar. Therefore, dose adaptation in elderly subjects is not considered necessary; however, care should be taken with dosing in elderly subjects as they may have impaired renal or hepatic function.

The difference in the occurrence of adverse events with tapentadol IR in men and women was similar to that observed with the active comparator oxycodone IR. In a thorough QT study, no effect of multiple therapeutic (100 mg) and multiple supratherapeutic (150 mg) doses of tapentadol IR on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Based on the pharmacology of tapentadol, the potential for abuse with tapentadol IR is consistent with currently marketed drugs such as hydromorphone, oxycodone, and morphine. Withdrawal symptoms
under tapentadol IR were only observed in the 1 clinical study with subject exposure up to 90 days, although termination of treatment in all studies was without tapering. These symptoms were usually classified as mild and were seen less frequently than in subjects randomized to oxycodone IR. No safety-relevant drug-drug interactions were seen. There was no death reported in subjects on tapentadol IR.

Pharmacovigilance system

Description of Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance (Version 3.0 dated 15 April 2010). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

Safety specification:
The following non-clinical safety concerns have been investigated: QT-prolongation, potential for abuse, convulsion, reproductive toxicity. Convulsions and reproductive toxicity will be accounted for in the SPC.

No risk of QT-prolongation was observed. Potential for abuse is acknowledged and regarded as comparable to other opioids. Convulsions and reproductive toxicity will be accounted for in the SPC.

A list of adverse reactions grouped by frequency and SOC observed in clinical trials is presented for both the immediate and the prolonged release formulation. Populations not studied or with limited data include mainly patients below the age of 18, pregnant and lactating women, patients with severe renal impairment, patients with clinically relevant hepatic impairment (Transaminases > 3 times ULN), patients on MAO inhibitors and patients with a history of drug or alcohol abuse. These aspects will be reflected in the relevant sections of the SPC.

As the product has not been launched prior to the finalization of this version of the RMP, no data on post-authorization usage is available.

No clinically relevant interactions were observed in the drug-drug interaction studies. Additive CNS depression is expected with other CNS depressants. Both will be stated in the SPC.

Pharmacological class effects of the group of µ-opioid receptor agonists include potential for abuse, convulsion, respiratory depression and bowel hypomobility. Compared to other opioids the risk of respiratory depression and bowel hypomobility is regarded as low.

A summary tabulation of ongoing safety concerns can be found below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Drug abuse and drug dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Convulsion</td>
</tr>
<tr>
<td>Important potential risks,</td>
<td>Overdose</td>
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<tr>
<td></td>
<td>Off-label use in pediatric patients</td>
</tr>
<tr>
<td></td>
<td>Potential for medication errors</td>
</tr>
<tr>
<td></td>
<td>Accidental exposure</td>
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<tr>
<td></td>
<td>Diversion</td>
</tr>
<tr>
<td>Important missing information</td>
<td>Use in pediatrics</td>
</tr>
</tbody>
</table>
Following the initial assessment the MAH agreed to replace the originally suggested important identified risk “Potential for abuse” by the more exact wording “Drug abuse and drug dependence”.

Pharmacovigilance Plan:
Apart from routine pharmacovigilance practices no additional pharmacovigilance activities have been suggested by the applicant. No additional studies are considered necessary by the applicant.

Risk minimization plan:
Apart from routine risk minimization activities (labeling, controlled drug status, inclusion into CCDS) no additional risk minimization activities have been proposed for the identified safety concerns. Thus no risk minimization plan is presented.

Summary of the risk management plan

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug abuse and drug dependence</td>
<td>Routine Pharmacovigilance practices are considered to be sufficient.</td>
<td>Appropriate labeling (Warning in section 4.4 and description in 4.9 of the CCDS) and the use of legal status of the drug as a controlled drug. No further risk minimization activities are identified as necessary or requested to date.</td>
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<tr>
<td>Overdose</td>
<td></td>
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<tr>
<td>Diversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td>Routine Pharmacovigilance practices are considered to be sufficient.</td>
<td>Appropriate labeling (Warning in section 4.4 of the CCDS). No further risk-minimization activities, other than labeling, has been conducted to date. No further risk-minimization activities are identified as necessary or requested to date.</td>
</tr>
<tr>
<td>Potential for medication errors</td>
<td>Routine Pharmacovigilance practices are considered to be sufficient.</td>
<td>Appropriate labeling. No further risk-minimization activities, other than labeling, has been conducted to date. No further risk-minimization activities are identified as necessary or requested to date.</td>
</tr>
<tr>
<td>Accidental exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in pediatrics</td>
<td>Routine Pharmacovigilance practices are considered to be sufficient.</td>
<td>Appropriate labeling. No further risk-minimization activities, other than labeling, has been conducted to date. No further risk-minimization activities are identified as necessary or requested to date. A development program to address the pediatric population is defined in the agreed PIP.</td>
</tr>
<tr>
<td>Off-label use in pediatric patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV. BENEFIT RISK ASSESSMENT
The benefit risk assessment is positive.
The application is approved.