Summary of pharmacokinetic parameters in monkeys after repeated i.v. administration of 5 mg/kg once daily (Mean ± SD on day 14)

Parameter		Mean ± SD
AUC	[ng·h/mL]	1035 ± 230
C_{max}	[ng/mL]	862 ± 111
t_{max}	[h]	0.22 ± 0.09
$t_{1/2,z}$	[h]	1.0 ± 0.2
CL	[mL/min/kg]	71.3 ± 14.8
V_z	[L/kg]	5.8 ± 0.2

3.3.4 Distribution

Tapentadol is rapidly and widely distributed in tissues. The volumes of distribution Vd values are 5-11 L/kg across species and in humans. Protein binding was low in all species in an radiolabeled drug-binding assay *in vitro* (Study PK582), primarily to serum albumin. Protein binding across the concentration range of 42.9 to 687 ng/ml was 16.3%-16.7% in mouse, 17.2%-18.5% in rat, 9.2%-12.0% in rabbit, 15.6%-18.9% in dog, and 19.3%-20.7% in human plasma. The results of that study also showed tapentadol binding to sepia melanin, at 26.7%-48.2%.

The results of a tissue distribution study using whole-body autoradiography in albino Sprague Dawley and pigmented Lister Hooded rats (Study PK432) given a single IV C^{14}-tapentadol (10 mg/kg) showed distribution to the following tissues at 15 minutes after treatment, in decreasing order of tissue concentration: kidney medulla and cortex, preputial gland, intra-orbital lachrymal gland, exorbital lachrymal gland, salivary glands, liver, Harderian gland, pituitary, pancreas, spleen, adrenal, lung, bone marrow, mandibular lymph nodes, bulbo-urethral gland, thyroid, brain, spinal cord, and blood. Fat and muscle concentrations were very low. The patterns of distribution were similar in the albino and pigmented species, except for melanin binding in ureal tract and skin tissues in the Hooded rats. Tapentadol levels in most of the tissues were below the level of quantification at 24 hours after IV injection in that study, and melanin-bound radioactivity decreased over the next 1-3 days. CNS levels decreased from peaks of 9.40 and 6.97 mcg equiv/g in brain and spinal cord at 0.25 h, to 4 mcg equiv/g in the CNS at 1 h, 1 mcg equiv/g at 2 h, 0.13 mcg equiv at 4 h, and were below the level of detection at 8 hours. There is a low potential for penetration of tapentadol and its metabolites into red blood cells. Comparison of radioactivity in whole blood and in serum revealed lower concentrations in whole blood than in the serum in dogs (-36%) and humans (-90% to -95%) administered C^{14}-tapentadol.

Tapentadol crosses the placenta, indicated by detection of the parent drug and the main glucuronide metabolite in albino rat fetuses in a dose range-finding study conducted prior to evaluation of Pre- and Post-Natal Development (Study TP2772, and PK432).

However, the concentrations measured in the fetuses were extremely low in that study, probably due in part to sampling times at 24 and 72 hours after the last maternal dose. A microdialysis study in Sprague Dawley rats administered non-labeled tapentadol at 6 oral gavage doses of 80 mg/kg each, 6 hours apart (Study PK664) demonstrated blood-brain penetration by the parent drug. Exposure to the parent drug in extracellular fluid in the corpus striatum was approximately half that in the peritoneal cavity samples collected to represent plasma concentration. Blood-brain penetration of the main glucuronide metabolite was lower, producing exposure of approximately 6% that in plasma following the first dose and 18% the plasma exposure after the last of the 6 doses. The results of that study are presented below (table provided from the original NDA submission):

	Pharmacokinetic parameters (mean ± Stand Dev)									
	AUC (h·ng/mL)		AUC ratio (ecf/pc)[a]		C_{max} (ng/mL)		$t_{1/2}$ (h)		MRT (h)	
After administration	1st	6th	1st	6th	1st	6th	1st	6th	1st	6th
Tissues / organs										
CG5503 base										
Peritoneal cavity	2220±2001	2499±1608			1084 ± 868	1046 ± 690	1.03 ± 0.55	1.57 ± 0.19	2.09 ± 0.58	2.34 ± 0.28
Extracellular fluid in the brain	979 ± 1284	1437±1002	0.44 ± 0.23	0.62 ± 0.18	441 ± 659	491 ± 453	0.99 ± 0.29	2.13 ± 1.49	2.18 ± 0.29	3.15 ± 1.51
Plasma	604 ± 217	2688±2762			478 ± 261	1602± 1484	1.21 ± 0.25	1.45 ± 0.50	2.06 ± 0.40	2.11 ± 0.42
CG5503 glucuronide										
Peritoneal cavity	47771±32147	673784±37524			16341±6334	31169±7343	0.57 ± 0.13	1.66 ± 1.11	2.43 ± 0.20	2.98 ± 0.15
Extracellular fluid in the brain	2634±1607	12485±7777	0.06 ± 0.03	0.18 ± 0.06	708.6±492.0	2464 ± 848	1.59 ± 0.57	2.45 ± 0.79	4.07 ± 0.52	4.07 ± 0.85
Plasma	45732±4872	61500±21755			12989±2696	16384±5715	1.49 ± 0.33	2.05 ± 1.08	3.14 ± 0.40	3.18 ± 1.24

3.3.5 Metabolism

Tapentadol is rapidly and extensively metabolized after oral administration. The results of *in vitro* evaluation in hepatic microsomes demonstrated that the main route of metabolism is by Phase II glucuronidation, in all species tested including humans (Study PKN233/A). The results of this study, showing the intrinsic clearance of tapentadol by O-glucuronidation and oxidation across species are presented below (table provided from the original NDA submission):

Species	Hamster	Minipig		Dog	Rabbit	Rat		Mouse	Cynomolgus		Guinea pig		Human
Sex	n.s.[a]	M	F	M	n.s.	M	F	n.s.	M	F	M	F	n.s.
Intrinsic clearances (ml/min/kg)[b]	0.1555	0.0800	0.0929	0.0425	0.0350	0.0244	0.0331	0.0117	0.0128	0.0108	0.0108	0.0088	0.0019
Sex	n.s.	n.s.		n.s.	n.s.	M	F	n.s.	n.s.		n.s.		n.s.
Percentual losses[c]	78.9	99.2		9.6	26.7	28.5	14.3	20.4	51.5		78.3		0.6
UGT[d]	1A1	1A3	1A4	1A6	1A9	2B7	2B15						
Percentages of glucuronide[e]	0.17	0.52	0.15	1.19	1.98	1.64	0.32						

Additional Information:Human hepatic glucuronidation was catalysed by several isoforms but mainly by UGT1A6, UGT1A9 and UGT2B7.

The fact that several isoforms appear to be involved in the glucuronidation of tapentadol means that there is little risk that its metabolic clearance will be diminished in humans who are homozygous for a deficient allele of one or other of the isoforms.

a) not specified

b) V_{max} / K_m [ml/min·mg] microsomal protein determined for glucuronidations by microsomes

c) Percentual losses of the initial amount of tapentadol in oxidation assays performed with equivalent amounts of P450 (300 pmol/ml), an initial concentration of 10 µM tapentadol and incubating for 30 min.

d) decombinant human glucuronyl transferase isoform

e) formed by various recombinant human glucuronyl transferase isoforms (UGTs) after 90 minutes

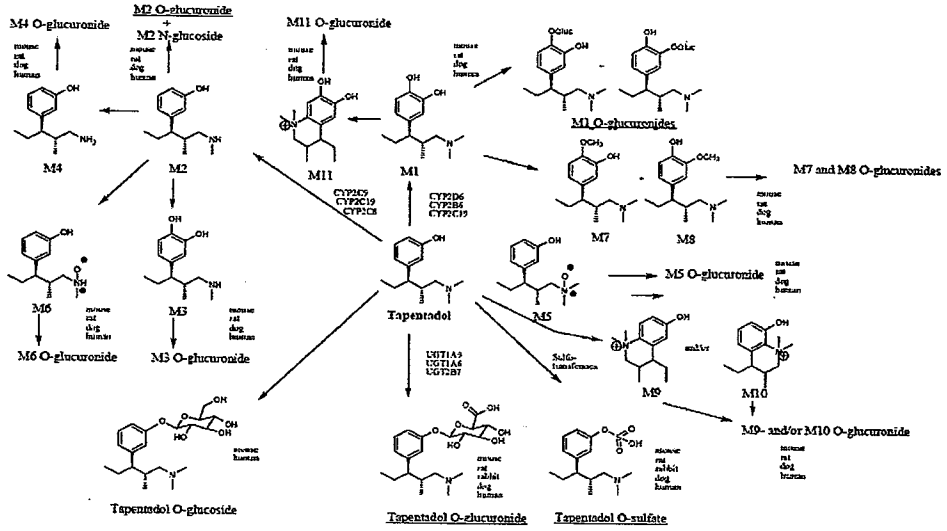
Tapentadol is more extensively glucuronidated in the animal species than in humans, based on the results of the study in hepatic microsomes. Oral bioavailability assessments in the nonclinical and clinical pharmacokinetic studies showed higher tapentadol bioavailability in human (32%) than in rat, dog and monkey (9%, 3% and <1%, respectively). The main metabolic enzymes involved in human tapentadol metabolism by glucuronidation are the UDP-glucuronosyltransferases UGT1A9, UGT2B7, and UGT1A6 (Study PK528). The percentages of glucuronide formed in human microsomes by the isoforms of UGT are shown in the following table (provided from the original NDA submission):

Table 4-2: Percentages of glucuronide formed by various recombinant human glucuronyl transferase isoforms (UGTs) after 90 minutes

UGT 1A1	UGT 1A3	UGT 1A4	UGT 1A6	UGT 1A9	UGT 2B7	UGT 2B15
0.17%	0.52%	0.15%	1.19%	1.98%	1.64%	0.32%

Additionally, tapentadol undergoes oxidation to a greater extent in the animal species tested than in humans. *In vivo* liver metabolism assay showed percent loss of tapentadol parent drug by hepatic microsomal P450 oxidation of 99.2% in minipig, 78.9% in hamster, 78.3% in guinea pig, 51.5% in Cynomolgus monkey, 28.5% in rat, 26.7% in rabbit, 20.4% in mouse, 14.3% in rat, 9.6% in dog, and 0.6% in human microsomes (Study PKN233/A). The Phase I metabolites were CYP2C9, CYP2C19, and CYP2C8 catalyzed N-demethyl tapentadol (M2), and hydroxy-tapentadol (M1) by CYP2D6, CYP2B6, and CYP2C19 catalysis, in microsomes from all species tested including human. Of all species tested, the metabolic profiles in rat and dog most resembled that in human.

The proposed tapentadol metabolic pathways in mice, rats, rabbits, dogs, and humans are diagramed in the following figure (provided from the original NDA submission):



The results of *in vivo* studies on tapentadol metabolism also showed qualitatively similar metabolic profiles in mice, rats, dogs and humans. HPLC analysis of urine samples collected over 48 hours in the animals and for 24 hours in humans after oral tapentadol administration (50 mg/kg in mice,150 mg/kg in rats, 20 mg/kg in dogs and 100 mg in human volunteers, given by gavage in the animal species) revealed the following results (table provided from the original NDA submission):

				% of Compound in Sample (mean values)				
Species	Sample	Sampling Time or Period (h)	% of Dose in Sample	Parent	Parent conjugates	M1con.	M2con.	Study No.
Mice	Urine	0-48	82	4.9	44	20	2.8	PK581K/A
	Feces	0-48	6.6	-	-	-	-	PK581K/A
Rat male	Urine	0-48	69	0.8	25	18	14	PK581K/A
	Feces	0-48	26	-	-	-	-	PK581K/A
Rat female	Urine	0-48	94	3.2	39	39	5	PK581K/A
	Feces	0-48	5	-	-	-	-	PK581K/A
Dogs	Urine	0-24	81[f]	<1	58	11	3.3	PK581K/A
	Feces	0-48	18	-	-	-	-	PK581K/A
Humans	Urine	0-24	99	4.5	70[h]	2	13	PK581K/A
	Feces	0-24	1	-	-	-	-	PK581K/A

a) quantitative investigations with HPLC and radiodetection of urine samples are from 3 males.
b) total dose
c) MBq/group
d) MBq/animal
e) MBq/kg body weight
f) capsule of 100 mg CG5503 labeled with 1.85 MBq radiocarbon
g) sampling Time is 0-48 h
h) tapentadol O-glucuronide: 55% of dose; tapentadol O-sulfate: 15% of dose

Total radioactivity in urine collected for 48 hours after a single oral dose was similar across species, when comparing data from several excretion studies (87%, 82%, 91%, and 90% in mice, rats, dogs and humans, respectively). In another comparative study on tapentadol metabolic profiles (PK581/A), the following pharmacokinetic parameters including excretion data were seen (table provided from the original NDA submission):

Species	Terminal half-life	Total clearance (i.v.)	Volume of distribution (i.v.)	Absolute bio-availability	Excretion of		
	$t_{1/2,z}$	CL	V_z	F	Total radioactivity		CG5503 base unchanged
	[h]	[mL/min·kg]	[L/kg]	[%]	[% of oral dose]		
					Urine	Feces	Urine unchanged
Mouse (M)	0.29 (i.v.) 0.64 (p.o.)	223	5.6	40	82	6.6	4.1
Rat (M/F)	0.5 (i.v.) >4 (p.o.)	228	10	9	70 (M) 94 (F)	26 (M) 4.9 (F)	0.8 (M) 3.2 (F)
Dog (M)	0.9 (i.v.) 3.7 (p.o.)	145	11	3	81	18	< 1.0
Monkey (M)[1)]	1.0 (i.v.)	71	5.8	< 1	n.d.	n.d.	n.d.
Human (M)	4.1 (i.v.) 1.25 (p.o.)	21	7.3	32 (fasted)	99	1.2	3.2

n.d. = not determined.

[1)] data after repeated i.v. or oral dosing

Minor metabolites (<5% total dose) are described in the figure on metabolic pathways of tapentadol, above. Nearly all (99.6% in dog and 96.6% in humans) of the eleven metabolites identified in plasma were found to be conjugated, with the remaining radioactivity associated with the parent drug.

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