CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213426Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA: 213426	Submission Date: 5/15/19
Relevant IND(s):	128177
Submission Type; Code:	505 (b) (2)
Generic Name:	Tramadol-celecoxib Co-crystal tablets
Reference Drugs:	Ultram (N020281 50 mg tablet for tramadol) and Celebrex (N020998 50, 100, 200 and 400 mg capsules for celecoxib)
Formulation; Strength(s):	Immediate-release tablets; 100mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	Esteve Pharmaceuticals
Proposed Indication:	Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Proposed Dosage Regimen:	• Use BRANDNAME for the shortest duration consistent with individual patient treatment goals. Initiate treatment of BRANDNAME with two tablets every 12 hours as needed for pain relief • When initiating treatment with BRANDNAME, take into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse • Moderate and Severe Hepatic Impairment: Not recommended • Severe Renal Impairment: Not recommended • Poor Metabolizers of CYP2C9 Substrates: Not recommended • Do not abruptly discontinue BRANDNAME in a physically-dependent patient

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1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application, NDA 213426, for tramadol-celecoxib CTC tablets, (BRANDNAME), submitted on 01/05/18. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable and no further communication is necessary with the Applicant. Based on the discussion in the wrap-up meeting, there are still outstanding review issues with other disciplines and whether the NDA will be approved is still pending. When this review is documented in DARRTS, the internal labeling meetings were held, however the labelling changes have not been negotiated with the applicant.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Esteve Pharmaceuticals submitted NDA 213426 for tramadol-celecoxib Co-crystal tablet (herein after interchangeably used as BRANDNAME or CTC tablet), under section 505 (b)(2) of the Federal Food Drug and Cosmetic Act. The two listed drugs for CTC tablets 505 (b)(2) application are Ultram (N020281, 50 mg tablet for tramadol) and Celebrex (N020998, 50, 100, 200 and 400 mg capsules for celecoxib). The BRANDNAME tablet is presented in 100 mg strength for oral administration. The proposed indication is similar to that of Ultram of management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

The proposed CTC 100 mg tablet contains 44 mg of tramadol hydrochloride and 56 mg of celecoxib. The proposed dosage is 2 tablets (2 x 100 mg CTC tablets that constitutes to a total dose of 88 mg of tramadol and 112 mg of celecoxib) every 12 hours. The maximum daily dosage is 400 mg (2 x 100 mg twice daily), that constitutes to a total daily dose of 176 mg of tramadol and 224 mg of celecoxib.

In support of this application, the Applicant has conducted three clinical pharmacology studies, one phase 2 dose-finding study, and one clinical safety and efficacy study. The clinical pharmacology studies evaluated, single-dose relative bioavailability (BA), multiple-dose relative BA and food-effect PK of CTC tablets.

An advisory committee meeting to discuss this the findings of this product was held on 01/15/2020. More details of the AC meeting can be found in the link https://www.fda.gov/advisory-committees/advisory-committee-calendar/january-15-2020-joint-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-and-drug.

The clinical pharmacology studies included a single-dose relative bioavailability (BA) study, a multiple-dose relative BA study, and a food effect pharmacokinetic (PK) study of CTC tablets. The purpose of these three studies was to evaluate single-dose and multiple-dose relative BA of CTC tablets compared to the reference drugs, and to evaluate food effect on CTC tablets. In addition, the effect of celecoxib on tramadol PK in the concomitant administration of tramadol and celecoxib was assessed using single and multiple dose relative BA studies. We conclude from these studies that:

1. After single dose administration, for the tramadol component of CTC tablets (total dose 88 mg), the Cmax was 30% lower and the AUCt and AUCinf were ~8% lower compared to Ultram tablets (total dose 100 mg). For the tramadol-M1 metabolite of CTC tablets, the Cmax was 30% lower and the AUCt and AUCinf were ~12% lower compared to Ultram tablets. For the celecoxib component of CTC tablets (total dose 112 mg), the Cmax was 15% lower and the AUCt and AUCinf was ~18% lower when compared to Celebrex 100 mg capsules. This single dose relative BA study established the scientific bridge to the reference drugs Ultram and Celebrex for this 505(b)(2) application.
2. After multiple dose administration of CTC tablets, the accumulation ratio of tramadol Cmax and AUCτ values (15^{th} dose/1^{st} dose) were 2.20-fold and 2.37-fold, respectively. The accumulation ratio of celecoxib Cmax and AUCτ values (15^{th} dose/1^{st} dose) were 1.80-fold and 2.17-fold, respectively. After multiple dosing, the Cmax,ss and AUC,ss values of tramadol and celecoxib components of CTC tablets were lower than the reference drugs, Adolonta* and Celebrex. Based on pre-dose concentrations, the steady state appears to be achieved for all three analytes, tramadol, M1 metabolite, and celecoxib, of CTC tablets.
3. When CTC tablets were administered under fed conditions, the AUC, Cmax, and Tmax of the tramadol component were not significantly affected. For the celecoxib component, the Tmax was delayed by approximately 2.5 hours and resulted in an approximate 30% increase in Cmax and AUC, which was similar to the food effect described in the Celebrex label. It is reasonable to recommend that CTC tablets be taken without regard to food.
4. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4. The formation of tramadol M1 metabolite is dependent on CYP2D6. In vitro studies indicate that celecoxib is an inhibitor of CYP2D6. In the concomitant administration of celecoxib and tramadol, the celecoxib does not appear to affect the PK of tramadol or its M1 metabolite either after single dose or multiple-dose.

* Adolonta (Tramadol 50 mg capsule) is not a US-approved drug. The applicant has established the required scientific bridge for this 505(b)(2) application via single-dose relative BA between CTC tablets and US approved reference drugs Ultram (Tramadol 50 mg tablets) and Celebrex (100 mg capsule). The PK comparison between CTC tablets and Adolonta capsules after multiple doses was used as supportive information and is not required to establish the scientific bridge.

Single dose relative BA of CTC tablets to reference drugs

Relative BA of tramadol and celecoxib of CTC tablets to reference drugs Ultram tablets (tramadol) and Celebrex capsule (celecoxib) was assessed in study ESTEVE-SUSA-101 or ETV-P5-669.

Treatments:

- Treatment 1: 200 mg (Test; 2 x CTC 100 mg tablets; 88 mg tramadol HCl and 112 mg celecoxib), administered alone
- Treatment 2: 100 mg (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl), administered alone
- Treatment 3: 100 mg (Reference-2; 1 x Celebrex 100 mg capsule), administered alone
- Treatment 4: 100 mg (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl) co-administered with 100 mg dose (Reference-2; 1 x Celebrex 100 mg capsule)

The plasma concentration time profiles of this study are shown in Section 2.4.1. The mean PK parameters of tramadol, its metabolite M1 (herein after called M1 in the text) and celecoxib of CTC tablets (test drug) versus Ultram tablets or Celebrex capsule (reference drugs) are shown in Table 1. The bioequivalence (BE) assessment is shown in Table 2.

Table 1: The mean PK parameters of tramadol, M1 and celecoxib parameters of CTC tablets (test drug) and Ultram tablets or Celebrex capsule (reference drugs)

Analyte	***Parameter Athematic Mean (% CV)***	***Trt 1****: Test 2 x CTC 100mg (88 mg tramadol + 112 mg celecoxib)*	***Trt 2:*** *Reference-1 2 x Ultram 50 mg (100 mg tramadol)*	***Trt 3:*** *Reference-2 1x Celebrex 100 mg*	***Trt-4:*** *Reference-1 2x Ultram 50 mg (100 mg tramadol) + Reference-2 1x Celebrex 100 mg*
		n=33	*n=32*	*n=33*	*n=32*
Tramadol	C_{max} (ng/mL)	214 (29)	305 (23)	-	312 (22)
	T_{max} (h) [$]	3.0 (1.25, 8.0)	2.0 (0.75, 3.0)	-	1.88 (1.0, 6.0)
	AUC_t (ng·h/mL)	2507 (36)	2709 (35)	-	2888 (34)
	AUC_∞ (ng·h/mL)	2590 (35) [a]	2802(32) [b]	-	2990 (32) [b]
	T½ (h)	6.5 (15)	6.1 (17)	-	6.2 (16)
Tramadol M1	C_{max} (ng/mL)	55 (29)	79 (29)	-	78 (29)
	T_{max} (h) [$]	4.0 (2.5, 8.0)	2.5 (1.25, 6.0)	-	2.5 (1.25, 8.0)
	AUC_t (ng·h/mL)	846 (27)	965 (25)	-	1010 (25)
	AUC_∞ (ng·h/mL)	879 (24) [a]	1002 (21) [b]	-	1049 (21) [b]
	T½ (h)	7.2 (14)	6.7 (14)	-	7.0 (15)
Celecoxib	C_{max} (ng/mL)	260 (34)	-	317 (47)	165 (46)
	T_{max} (h) [$]	1.5 (0.75, 6.0)	-	3.0 (1.25, 8.0)	2.5 (1.0, 12.0)
	AUC_t (ng·h/mL)	1930 (41)	-	2348 (40)	1929 (38)
	AUC_∞ (ng·h/mL)	2128 (42) [c]	-	2553 (43) [d]	2224 (39) [e]
	T½ (h)	13 (27)	-	11 (46)	14 (29)

[$] Median (minimum, maximum); [a] n=32, [b] n=31, [c] n=28, [d] n=27, [e] n=21

Table 2: Relative BA assessment of tramadol and celecoxib of CTC tablets versus Ultram tablets (tramadol) or Celebrex capsule (Celecoxib).

Tramadol PK parameter	**Geometric LS means**			**Comparison**	**Ratio**	**90% Confidence limits (%)**
	Trt 1: (N=33)	***Trt 2: (N=32)***	***Trt 4: (N=32)***			
Cmax (ng/mL)	205.10	296.00	304.15	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	**69.29** **67.43**	**66.24, 72.48** **64.47, 70.53**
AUCt (ng·h/mL)	2334.71	2528.69	2698.05	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	92.33 86.53	88.09, 96.77 82.56, 90.69
AUC∞ (ng·h/mL)	2424.32 [a]	2641.29 [b]	2816.85 [b]	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	91.79 86.06	87.64, 96.12 82.19, 90.13

Celecoxib PK parameter	**Geometric LS means**			**Comparison**	**Ratio**	**90% Confidence limits (%)**
	Trt 1: (N=33)	***Trt 3: (N=33)***	***Trt 4: (N=32)***			
Cmax (ng/mL)	244.29	286.92	153.44	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	85.14 **159.21**	**74.83**, 96.88 **139.74, 181.38**
AUCt (ng·h/mL)	1807.84	2208.09	1823.37	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	81.87 99.15	**77.27**, 86.75 93.51, 105.12
AUC∞ (ng·h/mL)	1988.53 [c]	2396.44 [d]	2107.10 [e]	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	82.98 94.37	**78.89**, 87.28 89.21, 99.83

[a] n=32, [b] n=31, [c] n=28, [d] n=27, [e] n=21

Relative BA comparison of tramadol and M1 of CTC tablet to Ultram tablets administered alone:

For tramadol component of CTC tablets (total dose 88 mg) (treatment 1), the Cmax was 30% lower and the AUCt and AUCinf were ~8% lower compared to Ultram tablets (total dose 100 mg) (treatment 2). In other words, a 12% lower dose of tramadol in CTC tablets (88 mg) results in 30% lower Cmax and 8% lower AUC compared to 100 mg of single-entity tramadol.

The median Tmax of tramadol of CTC tablets (3 h) was delayed by 1 h compared to Ultram tablets (2 h) (Table 1). When tramadol BE was assessed between CTC tablets and Ultram tablets, while tramadol AUCt and AUCinf, were within the 80-125% BE limits, the tramadol Cmax was outside the 80-125% BE limits (Table 2).

For M1 metabolite of CTC tablets (treatment 1), the Cmax was 30% lower and the AUCt and AUCinf were ~12% lower, and median Tmax was 1.5 h delayed compared to M1 of Ultram tablets (treatment 2) (Table 1).

Relative BA comparison of celecoxib of CTC tablet to Celebrex capsule administered alone:

For celecoxib component of CTC tablets (total dose 112 mg) (treatment 1), the Cmax was 15% lower and the AUCt and AUCinf was ~18% lower when compared to Celebrex 100 mg capsule (treatment 3). In other words, a 12% higher dose of celecoxib in CTC tablets (112 mg) results in 15% lower Cmax and 18% lower AUC compared to 100 mg of single-entity celecoxib.

The median Tmax of celecoxib of CTC (1.5 h) was 1.5 h earlier compared to Celebrex capsule (3 h) (Table 1). When celecoxib BE was assessed between CTC tablets and Ultram tablets, for all three celecoxib PK parameters (Cmax, AUCt and AUCinf) the lower bound of 90% CIs of geometric mean ratios (test/reference) were failed to be within 80-125% BE limits (Table 2).

Comparison of tramadol and celecoxib PK after concomitant administration of tramadol and celecoxib (treatment 4) to tramadol administered alone (treatment 2) or celecoxib administered alone (treatment 3) (drug-drug interaction):

The concomitant administration of tramadol and celecoxib results in no change in tramadol Cmax and AUC (~7% increase) compared to the tramadol administered alone.

The concomitant administration of tramadol and celecoxib results in 48% lower Cmax of celecoxib and 13% lower AUC of celecoxib compared to the celecoxib administered alone. The observed 48% lower Cmax of celecoxib in the concomitant administration treatment compared to the alone treatment does not appear to be metabolism related interaction, since celecoxib is primarily metabolized via CYP2C9 and tramadol is not known to be an inhibitor of CYP2C9. It may possibly absorption related, however, there is no data to support it.

Multiple dose relative BA versus reference drugs:

The multiple-dose relative BA of CTC tablets versus reference drugs was evaluated in study ESTEVE-SUSA-105.

Treatments administered:

Treatment 1:	2 x Test (CTC 100 mg tablets, total dose: 88 mg tramadol HCl; 112 mg celecoxib), administered 12 hours apart for a total of 15 consecutive doses.
Treatment 2:	2 x Reference-1 (Adolonta 50 mg capsules *, total dose: 100 mg tramadol HCl), administered 12 hours apart for a total of 15 consecutive doses.
Treatment 3:	1 x Reference-2 (Celebrex 100 mg capsule), administered 12 hours apart for a total of 15 consecutive doses.
Treatment 4:	2 x Reference-1 (Adolonta 50 mg capsules*, total dose: 100 mg tramadol HCl) plus 1 x Reference-2 (Celebrex 100 mg capsule), administered 12 hours apart for a total of 15 consecutive doses.

*Adolonta (Tramadol 50 mg capsule) is not a US-approved drug. The Applicant has established the required scientific bridge for this 505(b)(2) application via single-dose relative BA between CTC tablets and US approved reference drugs Ultram (Tramadol 50 mg tablets) and Celebrex (100 mg capsule). The PK comparison between CTC tablets and Adolonta capsules after multiple doses is shown as supportive information and is not required to establish the scientific bridge.

The mean plasma concentration time profiles after multiple dose are shown in Section 2.4.2.
The obtained PK parameters of CTC tablets and reference drugs after multiple dose administered 12 hours apart for a total of 15 consecutive doses are shown in Table 3.

Table 3: Mean PK parameters of CTC tablets and reference drugs after multiple dose, administered 12 hours apart for a total of 15 consecutive doses.

	PK Parameter Athematic Mean (% CV)	***Treatment 1: Test (2 x CTC 100mg tablets) (88 mg tramadol + 112 mg celecoxib) (N= 27)***			***Treatment 2 Reference-1 2x Adolonta 50 mg (100 mg Tramadol) (N= 28)***		***Treatment 3: Reference-2 1x Celebrex 100 mg (N= 27)***	***Treatment 4: Reference-1 2x Adolonta 50 mg (100 mg Tramadol) + Reference-2 1x Celebrex 100 mg (N= 27)***		
		Tramadol	***M1***	***Celecoxib***	***Tramadol***	***M1***	***Celecoxib***	***Tramadol***	***M1***	***Celecoxib***
Single dose	Cmax (ng/mL)	220 (25)	41 (45)	276 (39)	330 (16)	56 (48)	358 (37)	331 (21)	53 (46)	202 (37)
	Tmax (h) [$]	3.5 (1.0, 6.0)	4.0 (2.0, 12.0)	2.0 (0.5, 6.0)	1.75 (1.0, 4.0)	2.0 (1.0, 8.0)	3.0 (1.5, 8.0)	2.0 (1.0, 3.0)	3.0 (1.0, 8.0)	4.0 (1.0, 12.0)
	AUCτ (ng·h/mL)	1770 (27)	353 (42)	1442 (33)	2220 (25)	440 (40)	1929 (35)	2300 (24)	428 (41)	1256 (30)
Multiple dose	Cmax,ss (ng/mL) [a]	485 (22)	66 (37)	498 (27)	632 (24)	87 (34)	536 (33)	661 (25)	87 (35)	396 (34)
	Tmax,ss (hours)	3.0 (1.0, 6.0)	3.0 (1.5, 8.0)	2.0 (0.5, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)	2.0 (1.5, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)	3.0 (0.5, 6.0)
	AUCτ,ss (ng•h/mL) [b]	4201 (32)	637 (36)	3139 (28)	4990 (30)	791 (35)	3366 (27)	5284 (32)	734 (34)	2897 (31)
	Cavg (ng/mL) [c]	351 (32)	53 (36)	261 (28)	416 (30)	66 (35)	281 (27)	440 (32)	66 (34)	241 (31)
	T½ (hours)	9 (25)	10 (20)	13 (31)	9 (22)	10 (24)	10 (30)	9 (27)	9 5 (23)	12 (30)
	AUC∞ (ng·h/mL)	7749 (50)	1247 (35)	5810 (32)	8749 (48)	1468 (37)	5343 (34)	9350 (49)	1467 (37)	5823 (34)
	RA(Cmax) [d]	2.20	1.61	1.80	1 91	1.55	1.50	2.00	1.64	1 96
	RA(AUC) [e]	2.37	1.80	2 17	2 25	1.80	1.74	2.30	1.71	2 30

[$] Median (minimum, maximum) [$]

[a] Cmax,ss: Cmax after last multiple dose

[b] AUCτ,ss AUC over the dosing interval at steady state

[c] Cavg: average concentration over the doing interval, AUCτ,ss /12 h

[d] RA(Cmax): Accumulation ratio, mean Cmax,ss at steady state / mean Cmax after single dose.

[e] RA(AUC): Accumulation ratio, mean AUCτ,ss at steady state /mean AUCτ after single dose.

The mean pre-dose concentrations prior to the 13th, 14th and 15th doses of CTC tablets were 227, 229, and 239 ng/mL, respectively for tramadol; 42, 41, and 42 ng/mL, respectively for M1; and 173, 140, and 181 ng/mL, respectively for celecoxib. Based on pre-dose concentrations, the steady state appears to be achieved for all three analytes, tramadol, M1 and celecoxib of CTC tablets.

After multiple dosing of CTC tablets, the accumulation ratio of tramadol Cmax and AUCτ values (15th dose/ 1st dose) were 2.20-fold and 2.37-fold, respectively. The accumulation ratio of celecoxib Cmax and AUCτ values (15th dose/ 1st dose) were 1.80-fold and 2.17-fold, respectively.

Multiple dose relative BA comparison:

After multiple dosing, the Cmax,ss and AUC,ss values of tramadol of CTC tablets are 24% and 16% lower, respectively, compared to the Adolonta (tramadol) tablets administered alone. While , the Cmax,ss and AUC,ss values of celecoxib of CTC tablets are 10% and 7% lower, respectively compared to the Celebrex (celecoxib) administered alone.

After multiple dosing, there were no differences in the half-lives of tramadol and celecoxib of CTC tablets to reference drugs, Adolonta or Celebrex (Table 5).

DDI assessment: Effect of celecoxib on tramadol PK in the concomitant administration of tramadol and celecoxib after single and multiple dose:

Based on Celebrex label, the in vitro studies indicate that the celecoxib is an inhibitor of CYP2D6. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4. The formation of tramadol M1 metabolite is dependent on CYP2D6.

Since CYP2D6 is involved in the metabolism of tramadol, and celecoxib being an inhibitor of CYP2D6 based on in vitro data, the effect of celecoxib on tramadol PK in the concomitant administration of tramadol and celecoxib was assessed utilizing treatment 2 and treatment 4 arms of applicant's single dose and multiple-dose PK studies, ESTEVE-SUSA-101 and ESTEVE-SUSA-105, respectively.

Single Dose:

The single dose study demonstrates that the Cmax and AUC of tramadol and its metabolite M1 were not affected in the concomitant administration of celecoxib and tramadol in comparison to tramadol administered alone (Table 4). This can be noticed from the comparable PK profiles between two treatment arms (shown in Figure 2.3.2a).This indicates that celecoxib does not affect tramadol and M1 PK.

Table 4: The single-dose PK parameters of tramadol and M1 after 100 mg tramadol administered alone (Trt 2) and in combination with 100 mg celecoxib (Trt 4).

Analyte	*Parameter Athematic Mean (% CV)*	***Trt 2:*** *2 x Ultram 50 mg (100 mg tramadol)*	***Trt 4:*** *2x Ultram 50 mg (100 mg tramadol) + 1x Celebrex 100 mg*	***Ratio Trt 4/ Trt 2***
		n=32	*n=32*	
Tramadol	C_{max} (ng/mL)	305 (23)	312 (22)	1.02
	AUC_{∞} (ng·h/mL)	2802(32) [b]	2990 (32) [b]	1.07
Tramadol M1	C_{max} (ng/mL)	79 (29)	78 (29)	0.99
	AUC_{∞} (ng·h/mL)	1002 (21) [b]	1049 (21) [b]	1.05

[b] n=31

Multiple Dose:

The multiple dose study (BID dosing, total 15 doses) demonstrates that the steady-state Cmax and AUC of tramadol and its metabolite M1 were not affected in the concomitant administration of celecoxib and tramadol in comparison to tramadol administered alone (Table 5). This can be noticed from the comparable PK profiles between two treatment arms after multiple dose (shown in Figure 2.3.2b).This indicates that celecoxib does not affect tramadol and M1 PK under steady state conditions.

Table 5: The multiple-dose (BID dosing, total 15 doses) PK parameters of tramadol and M1 after 100 mg tramadol administered alone (Trt 2) and in combination with 100 mg celecoxib (Trt 4).

Analyte	*Parameter Athematic Mean (% CV)*	***Trt-2*** *2x Adolonta 50 mg (100 mg Tramadol)*	***Trt 4:*** *2x Adolonta 50 mg (100 mg Tramadol) + 1x Celebrex 100 mg*	***Ratio Trt 4/ Trt 2***
		n=28	*n=27*	
Tramadol	Cmax,ss (ng/mL) [a]	632 (24)	661 (25)	1.04
	AUCτ,ss (ng•h/mL) [b]	4990 (30)	5284 (32)	1.06
Tramadol M1	Cmax,ss (ng/mL) [a]	87 (34)	87 (35)	1.00
	AUCτ,ss (ng•h/mL) [b]	791 (35)	734 (34)	0.93

[a] Cmax,ss: Cmax after last multiple dose

[b] AUCτ,ss AUC over the dosing interval at steady state

Comments of DDI assessment:

In the concomitant administration of celecoxib and tramadol, although CYP2D6 is involved in the metabolism of tramadol; and celecoxib being a CYP2D6 inhibitor, the study results indicates that co-administration of celecoxib does not appear to affect the PK of tramadol or M1 either after single dose or multiple dose.

Food-effect assessment on CTC tablets:

Sponsor assessed the food-effect on CTC tablets (CTC fed versus CTC fasting) in Study ESTEVE-SACO4-104.

The mean plasma concentration time profiles are shown in Section 2.3.1. The mean PK parameters of tramadol, tramadol-M1 and celecoxib of CTC tablets administered under fed versus fasting conditions are shown in Table 6. The food-effect assessment is shown in Table 7.

Table 6: The mean PK parameters of tramadol, tramadol-M1 and celecoxib parameters of CTC tablets under fed versus fasting conditions.

	Athematic Mean (% CV)					
Parameter	***Tramadol***		***Tramadol M1 metabolite***		***Celecoxib***	
	Fed (n=33)	**Fasting (n=33)**	**Fed (n=33)**	**Fasting (n=33)**	**Fed (n=33)**	**Fasting (n=33)**
C_{max} (ng/mL)	267 (21)	244 (23)	56 (31)	53 (36)	526 (35)	410 (42)
T_{max} (hours) $	3.7 (1.75, 5.5)	2.7 (1.5, 6.0)	4.5 (2.3, 6.0)	4.0 (2.3, 8.0)	3.7 (1.0, 6.0)	1.25 (0.75, 6.0)
AUC_t (ng·h/mL)	2720 (34)	2773 (34)	764 (28)	803 (29)	4411 (58)	3450 (73)
AUC_∞ (ng·h/mL)	2802 (32)	2857 (32)	782 (27)	825 (28)	4514 (67)	3615 (81) *
T½ (hours)	6.1 (25)	6.6 (24)	6.7 (22)	7.4 (20)	8.2 (37)	11.3 (39) *

$ Median (minimum, maximum)

* n=30, terminal phase of celecoxib could not be adequately estimated in 3 subjects out of 33 subjects

Table 7: Food-effect assessment of CTC tablets (fed versus fasting conditions).

Analyte PK parameter	**Geometric LS means**		**Ratio**	**90% Confidence limits (%)**
Tramadol	**Fed state**	**Fasting state**		
Cmax (ng/mL)	261.05	236.40	110.43	105.34, 115.76
AUCt (ng·h/mL)	2570.81	2616.33	98.26	94.48, 102.20
AUC∞ (ng·h/mL)	2660.36	2704.35	98.37	94.85, 102.02
Tramadol M1 metabolite				
Cmax (ng/mL)	53.27	49.66	107.29	101.60, 113.30
AUCt (ng·h/mL)	733.18	768.41	95.41	92.40, 98.53
AUC∞ (ng·h/mL)	752.37	791.27	95.08	92.08, 98.19
Celecoxib				
Cmax (ng/mL)	499.47	381.54	**130.91**	116.98, **146.49**
AUCt (ng·h/mL)	4037.17	3065.13	**131.71**	124.54, **139.30**
AUC∞ (ng·h/mL)	4087.73	3160.35	**129.34**	121.78, **137.38**

For tramadol and M1, the food does not affect either Cmax or AUC. The point estimate of geometric mean ratios (fed/fasting) and corresponding 90% CIs for Cmax, AUCt and AUCinf of tramadol and its metabolite M1 were within the 80-125% BE limits. Under fed conditions, the median Tmax of tramadol and its metabolite M1 are delayed for 1-h and 0.5-h conditions, respectively compared to fasting conditions. Although median Tmax of Tramadol under fed conditions was slightly delayed compared to the fasting conditions, the range of individual Tmax (min, max) is comparable between fed (1.75 h, 5.5 h) and fasting conditions (1.75 h, 6.0 h) (Table 6)

For celecoxib component of CTC tablets, food increases Cmax and AUC approximately by 30% compared to the fasting conditions. Under fed conditions the median Tmax of celecoxib is delayed for ~2.5-h compared to fasting conditions.

Comments on food-effect:

When CTC tablets was administered under fed conditions, the AUC, Cmax and Tmax of tramadol component were not significantly affected. However, for celecoxib component, the Tmax was delayed approximately by ~2.5-h and Cmax and AUC resulted in around 30% increase for both parameters. The Celebrex label also reports that, under fed conditions the celecoxib Tmax was delayed 1 to 2 hours with 10 to 20% increase in AUC. The Celebrex label states that "Celebrex, at doses up to 200 mg twice daily, can be administered without regard to timing of meals."

For CTC tablets, since there was no food-effect on tramadol component and the food-effect on celecoxib component is approximately similar to Celebrex's food effect, it is reasonable recommend CTC tablets to be labeled to taken without regard to food.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Drug product

Celecoxib and Tramadol, Tablets has been developed as a combination of tramadol HCl and celecoxib where the API-API DS is a CTC that is formulated into immediate release tablets. The CTC contains 44% of tramadol hydrochloride and 56% celecoxib by weight; 100 mg contains 44 mg of tramadol hydrochloride and 56 mg of celecoxib. The maximum daily dose is 400 mg (200 mg twice a day).

The qualitative and quantitative composition of the proposed commercial formulation is described in Table 2.1.1 (Source 2.3.P.1, NDA).

Table 2.1.1: Description and Composition of the Drug Product

Name of the ingredients	Unit Composition % (w/w)	Unit Composition (mg)	Function	Amount per maximum Daily Dose (mg)	IIG Levels[1] (Oral tablet) (mg)	Quality standards
Drug substance						
Celecoxib-Tramadol, co-crystal[2]	(b) (4)	100.00	Drug substance	400.00	--	In-house (b) (4)
Excipients						
Sodium lauryl sulfate (b) (4						
Crospovidone (b) (4						
Mannitol (b) (4						
Sodium stearyl fumarate (b) (4						
Talc (b) (4						
Microcrystalline Cellulose (b) (4						

Copovidone (b) (4)		(b) (4)
Color mixture[4][5] (b) (4)		
Total (b) (4) *coated tablet (mg)*	*100.00*	(b) (4)

(b) (4)

2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

Tramadol:

Per Ultram label: Tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake. Although the mode of action is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound

Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.

Celecoxib:

Per Celebrex label: Celecoxib has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of CELEBREX is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2. Celecoxib is a potent inhibitor of prostaglandin synthesis in vitro. Celecoxib concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Since celecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

The proposed indication for BRANDNAME is for, 'management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate'

2.1.3 What are the proposed dosage and route of administration?

Proposed CTC 100 mg tablets are for oral administration that contains 44 mg of tramadol hydrochloride and 56 mg of celecoxib. The proposed dosage is 200 mg (2 x 100 mg CTC tablets that constitutes to 88 mg of tramadol and 112 mg of celecoxib) every 12 hours as needed for pain relief. The maximum daily dosage is 400 mg (2 x 100 mg twice daily), that constitutes to 176 mg of tramadol and 224 mg of celecoxib.

2.1.4 What are the core studies submitted in this NDA?

The following studies have been submitted in this NDA:

Clinical Pharmacology Studies:

- Study ESTEVE-SUSA-101 or ETV-P5-669: Relative BA study
    - A Single Dose 4-Way Crossover Bioavailability Study of Tramadol HCl and Celecoxib Following the Administration of CTC Tablets Versus the Drug Products Taken Individually or Concomitantly in Healthy Male and Female Volunteers / Fasting State
- Study ESTEVE-SACO4-104 or TAI-P1-585 or 80877: Food-effect study
    - A Single Dose Two-way Crossover Study to Assess the Effect of Food on the Bioavailability of Tramadol and Celecoxib Following Oral Administration of CTC Tablets in Healthy Male and Female Volunteers
- Study ESTEVE-SACO4-105 or TAI-P3-526 or 82608: Multiple dose study
    - A Single and Multiple Dose 4-Way Crossover Pharmacokinetic Study of Tramadol HCl and Celecoxib Following the Administration of CTC Tablets Versus the Drug Products Taken Individually or Concomitantly in Healthy Male and Female Volunteers/ Fasting State

Other two studies, ESTEVE-SACO4-103 and ESTEVE-SACO4-102 conducted by applicant are for formulation selection / EU comparator studies. These studies were not reviewed.

Clinical Studies:

- Study ESTEVE-SACO4-201: Phase 2 dose-finding study
    - A randomized, double-blind, controlled with active treatment (tramadol 100 mg) and placebo, parallel groups, Phase II clinical trial to establish the effective dose between 4 strengths of CTC Tablets for moderate to severe dental pain.
- Study ESTEVE-SUSA-301: Phase 3 Safety and Efficacy study
    - A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel Groups, Phase 3 Clinical Trial to Establish the Efficacy of CTC CTC Tablets for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Section 2.1.4 above shows the details of clinical pharmacology studies and phase 3 clinical study conducted for this NDA. Single-dose relative BA compared to reference drugs, multiple dose PK and food effect PK were evaluated for CTC tablets.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

CTC tablets contain tramadol and celecoxib. CTC analgesic activity is due to the tramadol, active metabolite of tramadol, M1 and celecoxib. All three moieties were measured in clinical pharmacology studies.

2.2.3 What are the general PK characteristics of the drug?

	Tramadol (Source: Ultram label)	Celecoxib (Source: Celebrex label)
Absolute bioavailability	75%	not conducted
Tmax	2 h (tramadol); 3 h (M1)	3 h
Steady state	within 2 days for both tramadol and M1	on or before day 5
Food effect	without regard to food	doses up to 200 mg without regard to food; doses > 400 mg with food to increase absorption
Protein binding	0.2 (20%)	0.97 (97%)
Metabolism	extensively metabolized by different pathways including CP2D6 and CYP3A4 followed by conjugation	CYP2C9
Elimination	metabolism and excretion in urine (30% of the dose as unchanged drug and 60% as metabolites)	By hepatic metabolism with <3% unchanged drug in urine and feces; 57% of the dose was excreted in the feces and 27% was excreted into the urine
Half-life	6.3 ± 1.4 (tramadol) 7.4 ± 1.4 (M1)	Variable 11.2 (effective half-life)
Hepatic Impairment	dosage adjustment in severe	moderate: 50% dose reduction severe: not recommended
Renal Impairment	dosage adjustment in severe	severe: not recommended
Geriatric	adjustment of the daily dose in patients > 75 years	adjustment of the daily dose in patients > 75 years
Pharmacogenomics	CYP2D6 genotype: in CYP2D6 poor metabolizers, 20% higher tramadol concentrations and 40% lower M1	CYP2C9 genotype: CYP2C9*3*3 shows 3- to 7-fold higher celecoxib levels than CYP2C9*1*1 or CYP2C9*1*3 (literature)

2.2.3.2. What are the characteristics of drug absorption? Are BRANDNAME tablets PK parameters dose proportional?

The details of tramadol and celecoxib components of CTC absorption can be noted from section 2.3.1 and 2.4.1. The PK dose linearity studies have not been conducted for CTC tablets, since it is available in single strength of 100 mg.

2.3 Extrinsic Factors

2.3.1 What is the effect of food on the BA of BRANDNAME tablets?

Sponsor assessed the food effect on CTC tablets (CTC fed versus CTC fasting) in Study ESTEVE-SACO4-104.

Identity of the Investigational Product:

- CTC 100 mg tablets batch # 810100 (Manufacturer: Laboratorios del Dr. Esteve S.A., Spain)

Treatments:

- Treatment 1: 2 x CTC 100 mg tablets (200 mg dose) under fed conditions
- Treatment 2: 2 x CTC 100 mg tablets (200 mg dose) under fasting conditions

Number of subjects in PK population: 33

Results:

The mean plasma concentration time profiles and mean PK parameters of tramadol, tramadol-M1 and celecoxib of CTC tablets administered under fed versus fasting conditions are shown in Figure 2.3.1 and Table 2.3.1a, respectively. The food-effect assessment is shown in Table 2.3.1b.

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Figure 2.3.1: The mean plasma concentration time profiles of tramadol, tramadol-M1 and celecoxib of CTC tablets under fed versus fasting conditions (n=33)

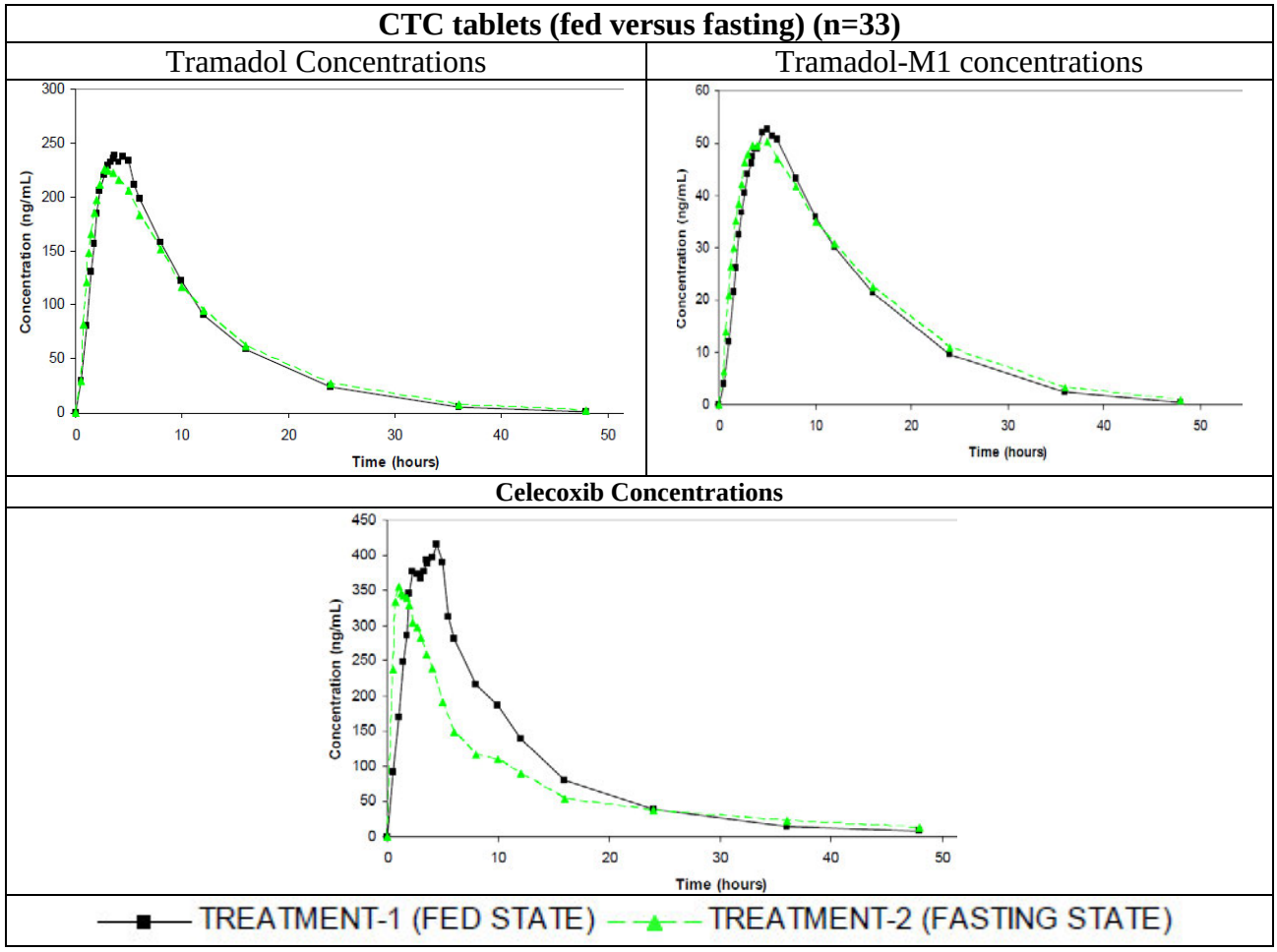


Table 2.3.1a: The mean PK parameters of tramadol, tramadol-M1 and celecoxib parameters of CTC tablets under fed versus fasting conditions.

	Athematic Mean (% CV)					
Parameter	***Tramadol***		***Tramadol M1 metabolite***		***Celecoxib***	
	Fed (n=33)	**Fasting (n=33)**	**Fed (n=33)**	**Fasting (n=33)**	**Fed (n=33)**	**Fasting (n=33)**
Cmax (ng/mL)	267 (21)	244 (23)	56 (31)	53 (36)	526 (35)	410 (42)
Tmax (hours) $	3.7 (1.75, 5.5)	2.7 (1.5, 6.0)	4.5 (2.3, 6.0)	4.0 (2.3, 8.0)	3.7 (1.0, 6.0)	1.25 (0.75, 6.0)
AUCt (ng·h/mL)	2720 (34)	2773 (34)	764 (28)	803 (29)	4411 (58)	3450 (73)
AUC∞ (ng·h/mL)	2802 (32)	2857 (32)	782 (27)	825 (28)	4514 (67)	3615 (81) *
T½ (hours)	6.1 (25)	6.6 (24)	6.7 (22)	7.4 (20)	8.2 (37)	11.3 (39) *

$ Median (minimum, maximum)

* n=30, terminal phase of celecoxib could not be adequately estimated in 3 subjects out of 33 subjects

Table 2.3.1b: Food-effect assessment of CTC tablets administered under fed versus fasting conditions.

Analyte PK parameter	**Geometric LS means**		**Ratio**	**90% Confidence limits (%)**
Tramadol	**Fed state**	**Fasting state**		
Cmax (ng/mL)	261.05	236.40	110.43	105.34, 115.76
AUCt (ng·h/mL)	2570.81	2616.33	98.26	94.48, 102.20
AUC∞ (ng·h/mL)	2660.36	2704.35	98.37	94.85, 102.02
Tramadol M1 metabolite				
Cmax (ng/mL)	53.27	49.66	107.29	101.60, 113.30
AUCt (ng·h/mL)	733.18	768.41	95.41	92.40, 98.53
AUC∞ (ng·h/mL)	752.37	791.27	95.08	92.08, 98.19
Celecoxib				
Cmax (ng/mL)	499.47	381.54	**130.91**	116.98, **146.49**
AUCt (ng·h/mL)	4037.17	3065.13	**131.71**	124.54, **139.30**
AUC∞ (ng·h/mL)	4087.73	3160.35	**129.34**	121.78, **137.38**

For tramadol and M1, the food does not affect either Cmax or AUC. The point estimate of geometric mean ratios (fed/fasting) and corresponding 90% CIs for Cmax, AUCt and AUCinf of tramadol and its metabolite M1 were within the 80-125% BE limits. Under fed conditions, the median Tmax of tramadol and its metabolite M1 are delayed for 1-h and 0.5-h conditions, respectively compared to fasting conditions. Although median Tmax of Tramadol under fed conditions was slightly delayed compared to the fasting conditions, the range of individual Tmax (min, max) is comparable between fed (1.75 h, 5.5 h) and fasting conditions (1.75 h, 6.0 h) (Table 3)

For celecoxib component of CTC tablets, food increases Cmax and AUC approximately by 30% compared to the fasting conditions. Under fed conditions the median Tmax of celecoxib is delayed for ~2.5-h compared to fasting conditions.

Comments on food-effect:

When CTC tablets was administered under fed conditions, the AUC, Cmax and Tmax of tramadol component were not significantly affected. However, for celecoxib component, the Tmax was delayed approximately by ~2.5-h and Cmax and AUC resulted in around 30% increase for both parameters. The Celebrex label also reports that, under fed conditions the celecoxib Tmax was delayed 1 to 2 hours with 10 to 20% increase in AUC. The Celebrex label states that "Celebrex, at doses up to 200 mg twice daily, can be administered without regard to timing of meals."

For CTC tablets, since there was no food-effect on tramadol component and the food-effect on celecoxib component is approximately similar to Celebrex's food effect, it is reasonable recommend CTC tablets to be labeled to taken without regard to food.

2.3.2 What is the effect of celecoxib on the tramadol PK (DDI assessment)?

Based on Celebrex label, the in vitro studies indicate that the celecoxib is an inhibitor of CYP2D6. Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4. The formation of tramadol M1 metabolite is dependent on CYP2D6.
Since CYP2D6 is involved in the metabolism of tramadol, and celecoxib being an inhibitor of CYP2D6 based on in vitro data, the effect of celecoxib on tramadol PK in the concomitant administration of tramadol and celecoxib was assessed utilizing treatment 2 and treatment 4 arms of applicant's single dose and multiple-dose PK studies, ESTEVE-SUSA-101 and ESTEVE-SUSA-105, respectively.

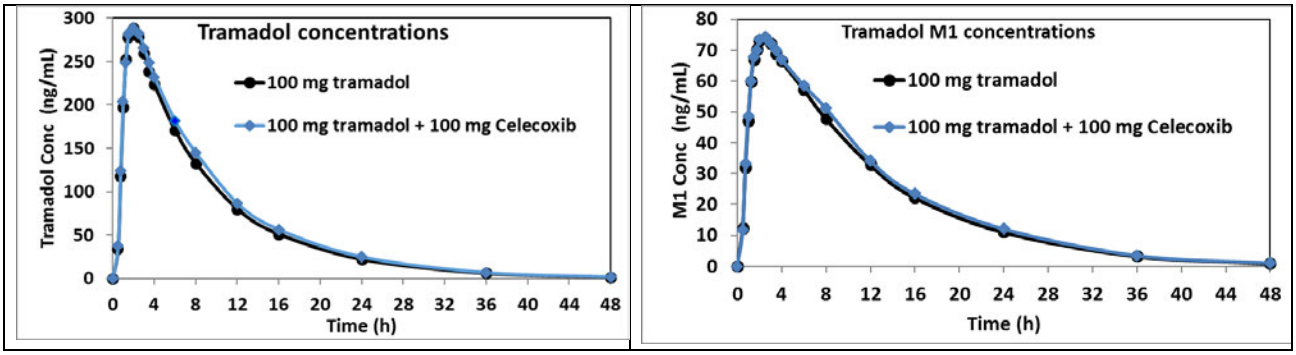
Single Dose:
The single dose study demonstrates that the Cmax and AUC of tramadol and its metabolite M1 were not affected in the concomitant administration of celecoxib and tramadol in comparison to tramadol administered alone (Table 2.3.2a). This can be noticed from the comparable PK profiles between two treatment arms (Figure 2.3.2a). This indicates that celecoxib does not affect tramadol and M1 PK.

Table 2.3.2a: The single-dose PK parameters of tramadol and M1 after tramadol 100 mg administered alone (Trt 2) and in combination with celecoxib 100 mg (Trt 4).

Analyte	*Parameter Athematic Mean (% CV)*	***Trt 2:*** *2 x Ultram 50 mg (100 mg tramadol)*	***Trt 4:*** *2x Ultram 50 mg (100 mg tramadol) + 1x Celebrex 100 mg*	***Ratio Trt 4/ Trt 2***
		n=32	*n=32*	
Tramadol	Cmax (ng/mL)	305 (23)	312 (22)	1.02
	AUC∞ (ng·h/mL)	2802(32) [b]	2990 (32) [b]	1.07
Tramadol M1	Cmax (ng/mL)	79 (29)	78 (29)	0.99
	AUC∞ (ng·h/mL)	1002 (21) [b]	1049 (21) [b]	1.05

[b] n=31

Figure 2.3.2 a: Mean plasma concentration time profiles of tramadol and tramadol-M1 after single dose administration of tramadol alone and tramadol with concomitant administration with celecoxib (n=32)



Multiple Dose:

The multiple dose study (BID dosing, total 15 doses) demonstrates that the steady-state Cmax and AUC of tramadol and its metabolite M1 were not affected in the concomitant administration of celecoxib and tramadol in comparison to tramadol administered alone (Table 2.3.2b). This indicates that celecoxib does not affect tramadol and M1 PK under steady state conditions for both drugs.

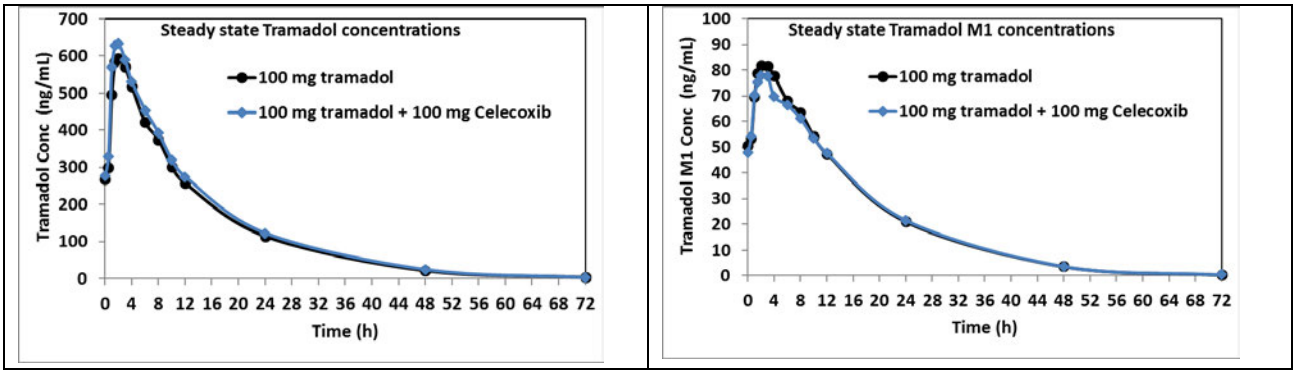
Table 2.3.2b: The multiple-dose (BID dosing, total 15 doses) PK parameters of tramadol and M1 after 100 mg tramadol administered alone (Trt 2) and in combination with 100 mg celecoxib (Trt 4).

Analyte	*Parameter Athematic Mean (% CV)*	***Trt-2*** *2x Adolonta 50 mg (100 mg Tramadol)*	***Trt 4:*** *2x Adolonta 50 mg (100 mg Tramadol) + 1x Celebrex 100 mg*	***Ratio Trt 4/ Trt 2***
		n=28	*n=27*	
Tramadol	Cmax,ss (ng/mL) [a]	632 (24)	661 (25)	1.04
	AUCτ,ss (ng•h/mL) [b]	4990 (30)	5284 (32)	1.06
Tramadol M1	Cmax,ss (ng/mL) [a]	87 (34)	87 (35)	1.00
	AUCτ,ss (ng•h/mL) [b]	791 (35)	734 (34)	0.93

[a] Cmax,ss: Cmax after last multiple dose

[b] AUCτ,ss AUC over the dosing interval at steady state

Figure 2.3.2 b: Mean steady state plasma concentration time profiles of tramadol and tramadol-M1 after multiple dose administration (BID dosing, total 15 doses) of tramadol alone and tramadol with concomitant administration with celecoxib (n=27)



Reviewer's Comments :

In the concomitant administration of celecoxib and tramadol, the celecoxib does not affect PK of tramadol and M1 both after single dose or multiple-dose as shown above. Although CYP2D6 is involved in the metabolism of tramadol; and celecoxib being a CYP2D6 inhibitor based on in vitro data, the study result indicates that co-administration of celecoxib does not appear to affect the PK of tramadol and M1. This observation may be due to 1) involvement of multiple CYP pathways in the metabolism of tramadol, or 2) because the obtained systemic celecoxib concentrations are not high enough to cause clinically significant interaction in vivo.

2.4 General Biopharmaceutics

2.4.1. What is the relative bioavailability of CTC tablets compared to the reference drugs Ultram and Celebrex?

Single dose relative BA of CTC tablets to reference drugs Ultram tablets (tramadol) and Celebrex capsule (celecoxib) was assessed in study ESTEVE-SUSA-101 or ETV-P5-669.

Identity of the Investigational Products:

- CTC 100 mg tablets, batch # 862110
- Ultram, 50 mg tablets, batch 16CG295
- Celebrex, 100 mg tablets, batch C150059

Treatments:

Treatment 1:	200 mg dose (Test; 2 x CTC 100 mg tablets; 88 mg tramadol HCl and 112 mg celecoxib), administered alone
Treatment 2:	100 mg dose (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl), administered alone
Treatment 3:	100 mg dose (Reference-2; 1 x Celebrex 100 mg capsule), administered alone
Treatment 4:	100 mg dose (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl) co-administered with 100 mg dose (Reference-2; 1 x Celebrex 100 mg capsule)

Results:

Mean plasma concentration time profiles and mean PK parameters of tramadol, tramadol-M1 and celecoxib of CTC tablets (test drug) versus Ultram tablets or Celebrex capsule (reference drugs) are shown in Figure 2.4.1 and Table 2.4.1a, respectively. The BE assessment is shown in Table 2.4.1b.

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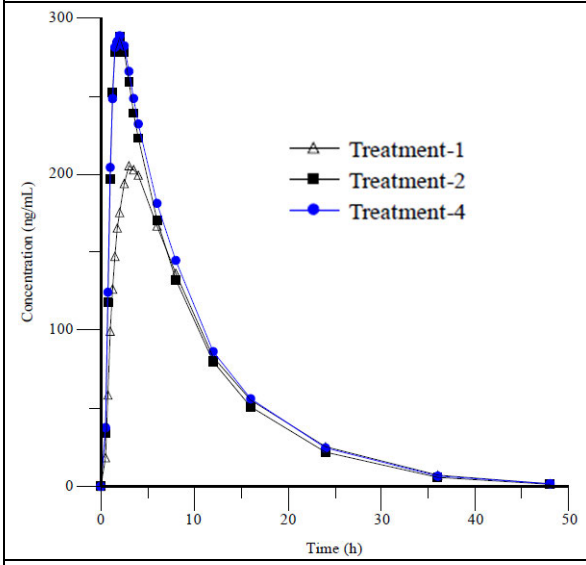
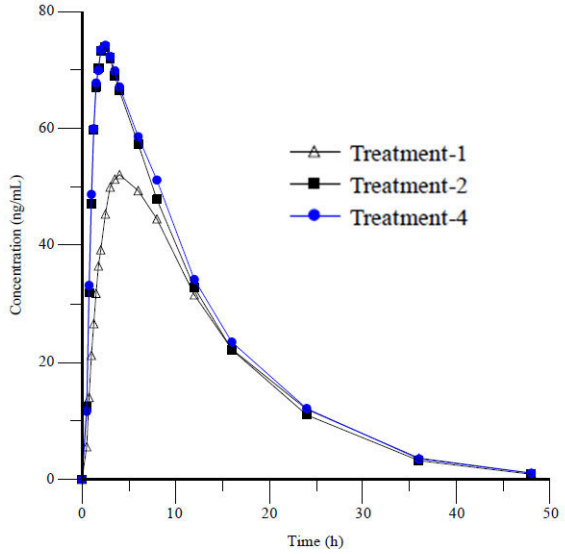
Figure 2.4.1: The mean plasma concentration time profiles of tramadol, tramadol-M1 and celecoxib of CTC tablets and Ultram tablets or Celebrex capsule (reference drugs)

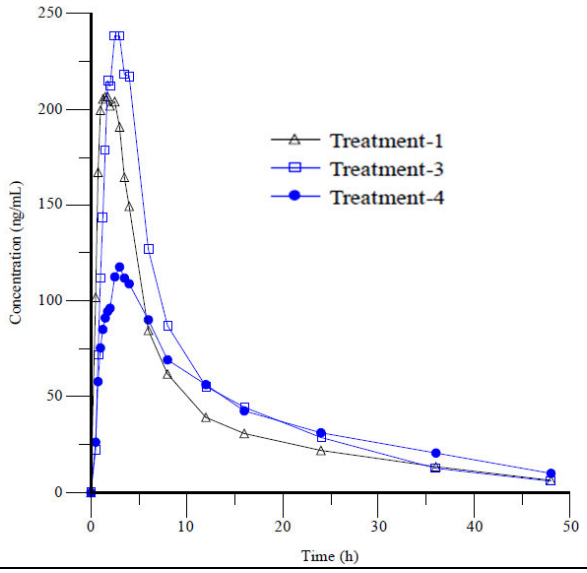
Tramadol Concentrations



Tramadol-M1 concentrations



Celecoxib Concentrations



Treatment 1: 200 mg dose (Test; 2 x CTC 100 mg tablets; 88 mg tramadol HCl and 112 mg celecoxib), administered alone
Treatment 2: 100 mg dose (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl), administered alone
Treatment 3: 100 mg dose (Reference-2; 1 x Celebrex 100 mg capsule), administered alone
Treatment 4: 100 mg dose (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl) co-administered with 100 mg dose (Reference-2; 1 x Celebrex 100 mg capsule)

Table 2.4.1a: The mean PK parameters of tramadol, tramadol-M1 and celecoxib parameters of CTC tablets (test drug) and Ultram tablets or Celebrex capsule (reference drugs)

Analyte	*Parameter Athematic Mean (% CV)*	***Trt 1****: Test 2 x CTC 100mg (88 mg tramadol + 112 mg celecoxib)*	***Trt 2:*** *Reference-1 2 x Ultram 50 mg (100 mg tramadol)*	***Trt 3:*** *Reference-2 1x Celebrex 100 mg*	***Trt-4:*** *Reference-1 2x Ultram 50 mg (100 mg tramadol) + Reference-2 1x Celebrex 100 mg*
		n=33	*n=32*	*n=33*	*n=32*
Tramadol	C_{max} (ng/mL)	214 (29)	305 (23)	-	312 (22)
	T_{max} (h) $	3.0 (1.25, 8.0)	2.0 (0.75, 3.0)	-	1.88 (1.0, 6.0)
	AUC_t (ng·h/mL)	2507 (36)	2709 (35)	-	2888 (34)
	AUC_∞ (ng·h/mL)	2590 (35) [a]	2802(32) [b]	-	2990 (32) [b]
	T½ (h)	6.5 (15)	6.1 (17)	-	6.2 (16)
Tramadol M1	C_{max} (ng/mL)	55 (29)	79 (29)	-	78 (29)
	T_{max} (h) $	4.0 (2.5, 8.0)	2.5 (1.25, 6.0)	-	2.5 (1.25, 8.0)
	AUC_t (ng·h/mL)	846 (27)	965 (25)	-	1010 (25)
	AUC_∞ (ng·h/mL)	879 (24) [a]	1002 (21) [b]	-	1049 (21) [b]
	T½ (h)	7.2 (14)	6.7 (14)	-	7.0 (15)
Celecoxib	C_{max} (ng/mL)	260 (34)	-	317 (47)	165 (46)
	T_{max} (h) $	1.5 (0.75, 6.0)	-	3.0 (1.25, 8.0)	2.5 (1.0, 12.0)
	AUC_t (ng·h/mL)	1930 (41)	-	2348 (40)	1929 (38)
	AUC_∞ (ng·h/mL)	2128 (42) [c]	-	2553 (43) [d]	2224 (39) [e]
	T½ (h)	13 (27)	-	11 (46)	14 (29)

$ Median (minimum, maximum); [a] n=32, [b] n=31, [c] n=28, [d] n=27, [e] n=21

Table 2.4.1b: BE assessment of tramadol and celecoxib of CTC tablets versus Ultram tablets (tramadol) or Celebrex capsule (Celecoxib).

Tramadol PK parameter	**Geometric LS means**			**Comparison**	**Ratio**	**90% Confidence limits (%)**
	Trt 1: (N=33)	***Trt 2: (N=32)***	***Trt 4: (N=32)***			
Cmax (ng/mL)	205.10	296.00	304.15	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	**69.29** **67.43**	**66.24, 72.48** **64.47, 70.53**
AUCt (ng·h/mL)	2334.71	2528.69	2698.05	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	92.33 86.53	88.09, 96.77 82.56, 90.69
AUC∞ (ng·h/mL)	2424.32 [a]	2641.29 [b]	2816.85 [b]	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	91.79 86.06	87.64, 96.12 82.19, 90.13

Celecoxib PK parameter	**Geometric LS means**			**Comparison**	**Ratio**	**90% Confidence limits (%)**
	Trt 1: (N=33)	***Trt 3: (N=33)***	***Trt 4: (N=32)***			
Cmax (ng/mL)	244.29	286.92	153.44	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	85.14 **159.21**	**74.83**, 96.88 **139.74, 181.38**
AUCt (ng·h/mL)	1807.84	2208.09	1823.37	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	81.87 99.15	**77.27,** 86.75 93.51, 105.12
AUC∞ (ng·h/mL)	1988.53 [c]	2396.44 [d]	2107.10 [e]	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	82.98 94.37	**78.89**, 87.28 89.21, 99.83

[a] n=32, [b] n=31, [c] n=28, [d] n=27, [e] n=21

Relative BA comparison of tramadol and M1 of CTC tablet to Ultram tablets administered alone:

For tramadol component of CTC tablets (total dose 88 mg) (treatment 1), the Cmax was 30% lower and the AUCt and AUCinf was ~8% lower compared to Ultram tablets (total dose 100 mg) (treatment 2). In other words, a 12% lower dose of tramadol in CTC tablets (88 mg) results in 30% lower Cmax and 8% lower AUC compared to 100 mg of single-entity tramadol.

The median Tmax of tramadol of CTC tablets (3 h) was delayed by 1 h compared to Ultram tablets (2 h) (Table 2.4.1a). When tramadol BE was assessed between CTC tablets and Ultram tablets, while tramadol AUCt and AUCinf, were within the 80-125% BE limits, the tramadol Cmax was outside the 80-125% BE limits (Table 2.4.1b).

For tramadol M1 metabolite of CTC tablets (treatment 1), the Cmax was 30% lower and the AUC (AUCt and AUCinf) was ~12% lower, and median Tmax was 1.5 h delayed compared to M1 metabolite of Ultram tablets (treatment 2) (Table 2.4.1b).

Relative BA comparison of celecoxib of CTC tablet to Celebrex capsule administered alone:

For celecoxib component of CTC tablets (total dose 112 mg) (treatment 1), the Cmax was 15% lower and AUCt and AUCinf was ~18% lower when compared to Celebrex 100 mg capsule (treatment 3). In other words, a 12% higher dose of celecoxib in CTC tablets (112 mg) results in 15% lower Cmax and 18% lower AUC compared to 100 mg of single-entity celecoxib

The median Tmax of celecoxib of CTC (1.5 h) was 1.5 h earlier compared to Celebrex capsule (3 h) (Table 2.4.1a). When celecoxib BE was assessed between CTC tablets and Ultram

tablets, for all three celecoxib PK parameters (Cmax, AUCt and AUCinf) the lower bound of 90% CIs of geometric mean ratios (test/reference) were failed to be within 80-125% BE limits (Table 2.4.1b).

Comparison of tramadol and celecoxib PK after concomitant administration of tramadol and celecoxib (treatment 4) to tramadol administered alone (treatment 2) or celecoxib administered alone (treatment 3) (drug-drug interaction):

The concomitant administration of tramadol and celecoxib results in comparable tramadol and M1 Cmax and AUC values compared to the single-entity tramadol administered alone.

The concomitant administration of tramadol and celecoxib results in 48% lower Cmax of celecoxib and 13% lower AUC of celecoxib compared to the celecoxib administered alone. The observed 48% lower Cmax of celecoxib in the concomitant administration treatment compared to the alone treatment does not appear to be metabolism related interaction, because celecoxib is primarily metabolized via CYP2C9 and tramadol is not known to be an inhibitor of CYP2C9. It may be possibly absorption related, however, there is no data to support it.

2.4.2: What is the multiple dose pharmacokinetic parameters of CTC tablets

The multiple-dose PK of CTC tablets was evaluated in study ESTEVE-SUSA-105. This study also evaluates the multiple-dose relative BA between CTC tablets and Adolonta* (tramadol) and Celebrex (celecoxib).

*Adolonta (Tramadol 50 mg capsule) is not a US-approved drug. The Applicant has established the required scientific bridge for this 505(b)(2) application via single-dose relative BA between CTC tablets and US approved reference drugs Ultram (Tramadol 50 mg tablets) and Celebrex (100 mg capsule). The PK comparison between CTC tablets and Adolonta capsules after multiple doses is shown as supportive information and is not required to establish the scientific bridge.

Title of Study:

A Single and Multiple Dose 4-Way Crossover Pharmacokinetic Study of Tramadol HCl and Celecoxib Following the Administration of CTC Versus the Drug Products Taken Individually or Concomitantly in Healthy Male and Female Volunteers/ Fasting State.

Identity of the Investigational Products:

- CTC 100 mg tablets, batch # 830042 (Manufacturer: Laboratorios del Dr. Esteve S.A., Spain)
- Celebrex, D10004536 P (Manufacturer: Pfizer Manufacturing Deutschland GmbH, Germany)

Treatments:

Treatment 1:	2 x Test (CTC 100 mg tablets, total dose: 88 mg tramadol HCl; 112 mg celecoxib), administered BID, 12 hours apart for a total of 15 consecutive doses.
Treatment 2:	2 x Reference-1 (Adolonta 50 mg capsules *, total dose: 100 mg tramadol HCl), administered BID, 12 hours apart for a total of 15 consecutive doses.
Treatment 3:	1 x Reference-2 (Celebrex 100 mg capsule), administered BID, 12 hours apart for a total of 15 consecutive doses.
Treatment 4:	2 x Reference-1 (Adolonta 50 mg capsules*, total dose: 100 mg tramadol HCl) plus 1 x Reference-2 (Celebrex 100 mg capsule), administered BID, 12 hours apart for a total of 15 consecutive doses.

Results:

Mean plasma concentration time profiles of tramadol, tramadol-M1 and celecoxib of CTC tablets (test drug) administered 12 hours apart for a total of 15 consecutive doses (treatment 1) are shown in Figure 2.4.2a.

The mean steady state plasma concentration time profiles of tramadol, tramadol-M1 and celecoxib of CTC tablets (test drug) and Adolonta tablets or Celebrex capsule (reference drugs) administered 12 hours apart, for a total of 15 consecutive doses shown in Figure 2.4.2b.

The obtained PK parameters of CTC tablets and reference drugs after multiple dose administered 12 hours apart for a total of 15 consecutive doses are shown in 2.4.2.

Figure 2.4.2a: Mean plasma concentration time profiles of tramadol, tramadol-M1 and celecoxib of CTC tablets (test drug) administered 12 hours apart, for a total of 15 consecutive doses.

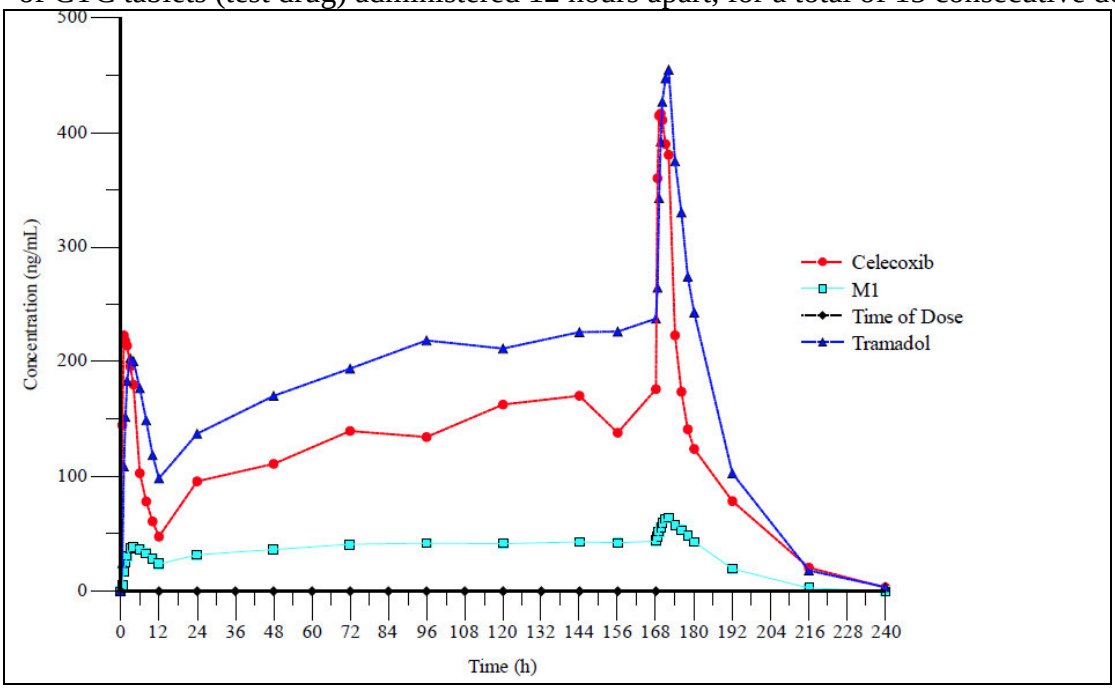
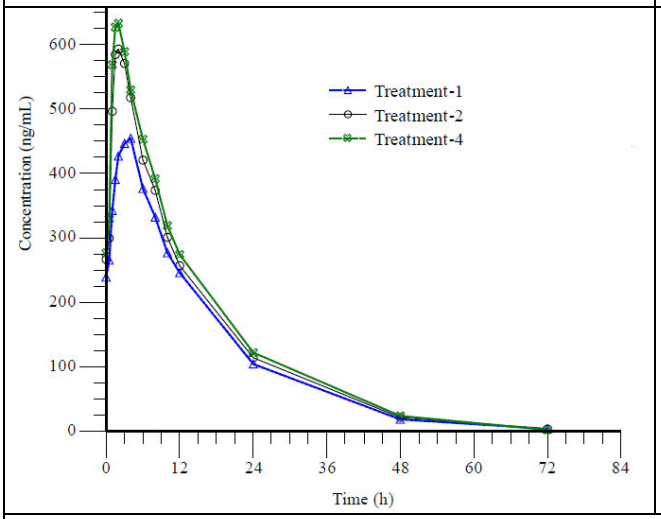
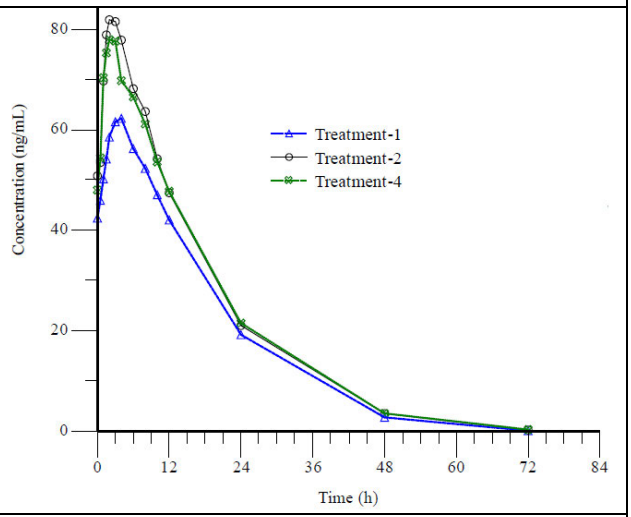


Figure 2.4.2b: The mean steady state plasma concentration time profiles of tramadol, tramadol-M1 and celecoxib of CTC tablets (test drug) and Adolonta tablets or Celebrex capsule (reference drugs) administered 12 hours apart, for a total of 15 consecutive doses.

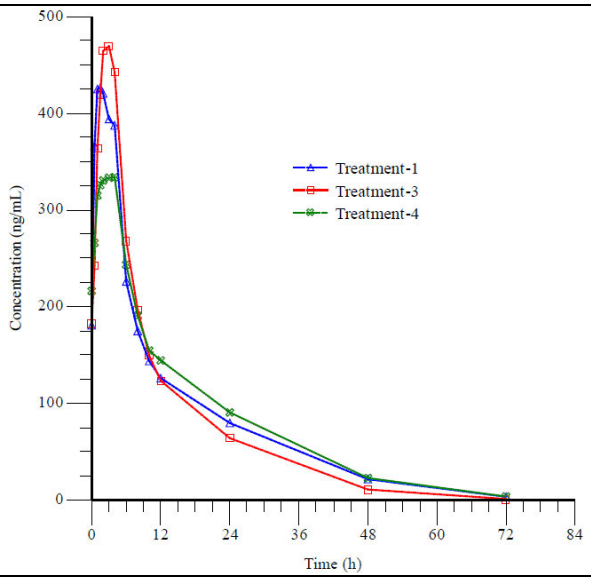
Tramadol Concentrations



Tramadol-M1 concentrations



Celecoxib Concentrations



Treatment 1: 2 x Test (CTC 100 mg tablets, total dose: 88 mg tramadol HCl; 112 mg celecoxib), administered 12 hours apart for a total of 15 consecutive doses.

Treatment 2: 2 x Reference-1 (Adolonta 50 mg capsules *, total dose: 100 mg tramadol HCl), administered 12 hours apart for a total of 15 consecutive doses.

Treatment 3: 1 x Reference-2 (Celebrex 100 mg capsule), administered 12 hours apart for a total of 15 consecutive doses.

Treatment 4: 2 x Reference-1 (Adolonta 50 mg capsules*, total dose: 100 mg tramadol HCl) plus 1 x Reference-2 (Celebrex 100 mg capsule), administered 12 hours apart for a total of 15 consecutive doses.

Table 2.4.2: Mean PK parameters of tramadol, tramadol-M1 and celecoxib of CTC tablets (test drug) administered BID, 12 hours apart for a total of 15 consecutive doses.

	PK Parameter Athematic Mean (% CV)	***Treatment 1: Test (2 x CTC 100mg tablets) (88 mg tramadol + 112 mg celecoxib) (N= 27)***			**Treatment-2** ***Reference-1 2x Adolonta 50 mg (100 mg Tramadol) (N= 28)***		***Treatment 3: Reference-2 1x Celebrex 100 mg (N= 27)***	***Treatment 4: Reference-1 2x Adolonta 50 mg (100 mg Tramadol) + Reference-2 1x Celebrex 100 mg (N= 27)***		
		Tramadol	***M1***	***Celecoxib***	***Tramadol***	***M1***	***Celecoxib***	***Tramadol***	***M1***	***Celecoxib***
Single dose	Cmax (ng/mL)	220 (25)	41 (45)	276 (39)	330 (16)	56 (48)	358 (37)	331 (21)	53 (46)	202 (37)
	Tmax (h) [$]	3.5 (1.0, 6.0)	4.0 (2.0, 12.0)	2.0 (0.5, 6.0)	1.75 (1.0, 4.0)	2.0 (1.0, 8.0)	3.0 (1.5, 8.0)	2.0 (1.0, 3.0)	3.0 (1.0, 8.0)	4.0 (1.0, 12.0)
	AUCτ (ng·h/mL)	1770 (27)	353 (42)	1442 (33)	2220 (25)	440 (40)	1929 (35)	2300 (24)	428 (41)	1256 (30)
Multiple dose	Cmax,ss (ng/mL) [a]	485 (22)	66 (37)	498 (27)	632 (24)	87 (34)	536 (33)	661 (25)	87 (35)	396 (34)
	Tmax,ss (hours)	3.0 (1.0, 6.0)	3.0 (1.5, 8.0)	2.0 (0.5, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)	2.0 (1.5, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)	3.0 (0.5, 6.0)
	AUCτ,ss (ng•h/mL) [b]	4201 (32)	637 (36)	3139 (28)	4990 (30)	791 (35)	3366 (27)	5284 (32)	734 (34)	2897 (31)
	Cavg (ng/mL) [c]	351 (32)	53 (36)	261 (28)	416 (30)	66 (35)	281 (27)	440 (32)	66 (34)	241 (31)
	T½ (hours)	9 (25)	10 (20)	13 (31)	9 (22)	10 (24)	10 (30)	9 (27)	9.5 (23)	12 (30)
	AUC∞ (ng·h/mL)	7749 (50)	1247 (35)	5810 (32)	8749 (48)	1468 (37)	5343 (34)	9350 (49)	1467 (37)	5823 (34)
	RA(Cmax) [d]	2.20	1.61	1.80	1.91	1.55	1 50	2.00	1.64	1.96
	RA(AUC) [e]	2.37	1.80	2.17	2.25	1.80	1.74	2.30	1.71	2.30

[$] Median (minimum, maximum) [$]

[a] Cmax,ss: Cmax after last multiple dose

[b] AUCτ,ss AUC over the dosing interval at steady state

[c] Cavg: average concentration over the doing interval, AUCτ,ss /12 h

[d] RA(Cmax): Accumulation ratio, Cmax,ss at steady state /Cmax after single dose.

[e] RA(AUC): Accumulation ratio, AUCτ,ss at steady state /AUCτ after single dose.

The mean pre-dose concentrations of tramadol prior to the 13th, 14th and 15th doses of were 227, 229, and 239 ng/mL, respectively whereas for tramadol -M1, they were 42, 41, and 42 ng/mL, respectively. The mean pre-dose concentration of celecoxib prior to the 13th, 14th and 15th doses were 173, 140, and 181 ng/mL, respectively. Based on pre-dose concentrations, the steady state appears to be achieved for all three analytes, tramadol, M1 and celecoxib of CTC tablets.

After multiple dosing of CTC tablets, the accumulation ratio of tramadol Cmax and AUCτ values (15th dose/ 1st dose) were 2.2-fold and 2.37-fold, respectively. The accumulation ratio of celecoxib Cmax and AUCτ values (15th dose/ 1st dose) were 1.80-fold and 2.17-fold, respectively.

Multiple dose relative BA comparison:

After multiple dosing, the Cmax,ss and AUC,ss values of tramadol of CTC tablets are 24% and 16% lower, respectively, compared to the Adolonta (tramadol) tablets administered alone. While , the Cmax,ss and AUC,ss values of celecoxib of CTC tablets are 10% and 7% lower, respectively compared to the Celebrex (celecoxib) administered alone.

After multiple dosing, there were no differences in the half-lives of tramadol and celecoxib of CTC tablets to reference drugs, Adolonta or Celebrex (Table 2.4.2).

Multiple Dose: Comparison of tramadol and celecoxib PK after concomitant administration of tramadol and celecoxib (treatment 4) to tramadol administered alone (treatment 2) or celecoxib administered alone (treatment 3) (drug-drug interaction):

The concomitant multiple dose administration of tramadol and celecoxib results in comparable tramadol and M1 Cmax,ss and AUCτ,ss values compared to the single-entity multiple dose tramadol administered alone.

The concomitant multiple dose administration of tramadol and celecoxib results in 26% lower Cmax,ss of celecoxib and 14% lower AUCτ,ss of celecoxib compared to the celecoxib administered alone. The magnitude of reduced Cmax is lower after multiple dose (26% lower) compared to the single dose (48% lower, Section 2.4.1).

The observed 26% lower Cmax of celecoxib in the concomitant multiple dose administration treatment compared to the alone treatment does not appear to be metabolism related interaction, because celecoxib is primarily metabolized via CYP2C9 and tramadol is not known to be an inhibitor of CYP2C9. It may be possibly absorption related, however, there is no data to support it.

2.6 Analytical Section

2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

PK Study, ESTEVE-SUSA-101 (single dose relative BA):

- Clinical: Algorithme Pharma USA LLC, Fargo, ND
- Bio-analytical: (b) (4)

  - The plasma concentrations of celecoxib, tramadol, and tramadol-M1 (O-desmethyl tramadol) were analyzed using validated HPLC-MS/MS assays.
    - The lower and upper limit of calibrator concentrations, and individual QC concentrations are as follows:

	Celecoxib (ng/mL)	Tramadol (ng/mL)	*M1* (ng/mL)
Calibrators	3 to 2400	2 to 800	0.5 to 200
QCs	3, 9, 200, 1200 and 1800	2, 6, 100 and 600	0.5, 1.5, 20 and 150

    - Accuracy and Precision over the range:
      - Accuracy (expressed as % bias): < ± 15%
      - Precision (expressed as % CV): < 15%

  - Internal Standards: Tramadol-D6 and Celecoxib-D7

- Long Term Stability: The duration of sample storage was 51 days. The first sample collection was on 2016/10/29 and last date of sample extraction was 2016/12/19.
    - The long-term stability of tramadol and M1 in the presence of celecoxib in human plasma covers 56 days at -20°C nominal. The long-term stability of M1 in the presence of M1 glucuronide in human plasma covers 391 days at -20°C nominal
- Incurred sample reanalysis: Passed

ESTEVE-SUSA-105 (Multiple dose relative BA) and ESTEVE-SACO4-104 (Food-effect):

- Bio-analytical: ESTEVE Av. Mare de Déu de Montserrat, 221 Barcelona Spain
    - The plasma concentrations of celecoxib, tramadol, and tramadol-M1 (O-desmethyl tramadol) were analyzed using validated HPLC-MS/MS assays.
        - The lower and upper limit of calibrator concentrations, and individual QC concentrations are as follows:

	Celecoxib (ng/mL)	Tramadol (ng/mL)	M1 (ng/mL)
Calibrators	2.5 to 1250	4 to 800	1 to 200
QCs	2.5, 5, 500 and 1000	4, 8, 200 and 600	1, 2, 50 and 150

        - Accuracy and Precision over the range:
            - Accuracy (expressed as % bias): < ± 15%
            - Precision (expressed as % CV): < 15%
        - Internal Standards: Tramadol-D6, O-Desmethyl Tramadol-D6 and Celecoxib-D7
        - Long Term Stability: Long-term in human plasma at -80ºC and -20ºC for 68 and 154 days for celecoxib and tramadol.
        - Incurred sample reanalysis: Passed

3 Labeling Comments:

The labelling changes have been made to the following sections in the Label:

7 DRUG INTERACTIONS

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Drug Interaction Studies

Tramadol and Celecoxib:

Tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4. The formation of tramadol M1 metabolite is dependent on CYP2D6. In vitro studies indicate that celecoxib is an inhibitor of CYP2D6.

An in vivo multiple dose PK study of 100 mg tramadol (2x50 mg) and 100 mg celecoxib (1x100 mg) administered concomitantly twice daily for 15 doses demonstrates that steady-state Cmax and AUC of tramadol and its active metabolite M1 are comparable along with comparable PK profiles to the 100 mg tramadol (2x50 mg) administered alone twice daily for 15 doses. The study results indicate that co-administration of celecoxib does not appear to affect the PK of tramadol or M1.

4.1 Study Designs:

Clinical Pharmacology Studies:

Study ESTEVE-SUSA-101 or ETV-P5-669: Relative BA study

- A Single Dose 4-Way Crossover Bioavailability Study of Tramadol HCl and Celecoxib Following the Administration of Co-crystal E-58425 Versus the Drug Products Taken Individually or Concomitantly in Healthy Male and Female Volunteers / Fasting State

Study ESTEVE-SACO4-104 or TAI-P1-585 or 80877: Food-effect study

- A Single Dose Two-way Crossover Study to Assess the Effect of Food on the Bioavailability of Tramadol and Celecoxib Following Oral Administration of E-58425 in Healthy Male and Female Volunteers

Study ESTEVE-SACO4-105 or TAI-P3-526 or 82608: Multiple dose study

- A Single and Multiple Dose 4-Way Crossover Pharmacokinetic Study of Tramadol HCl and Celecoxib Following the Administration of E-58425 Versus the Drug Products Taken Individually or Concomitantly in Healthy Male and Female Volunteers/ Fasting State

Clinical Studies:

Study ESTEVE-SACO4-201: Phase 2 dose-finding study

- A randomized, double-blind, controlled with active treatment (tramadol 100 mg) and placebo, parallel groups, Phase II clinical trial to establish the effective dose between 4 strengths of E-58425 for moderate to severe dental pain.

Study ESTEVE-SUSA-301: Phase 3 Safety and Efficacy Study

- A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel Groups, Phase 3 Clinical Trial to Establish the Efficacy of Co-crystal E-58425 for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy

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/s/

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