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Randomized comparative bioavailability of a novel 3D printed fast melt formulation of levetiracetam following the administration of a single 1000 mg dose to healthy human volunteers under fasting and fed conditions

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PURPOSE

- Levetiracetam, a second generation antiepileptic drug, is rapidly and almost completely absorbed (>95%) following oral administration, and exhibits linear pharmacokinetics (PK) over a 500 to 5000 mg dose range.
- Poor adherence to therapy and difficulty in swallowing represent barriers to medication adherence in the young, elderly and special populations (i.e., psychiatric, stroke, CP, autism, dysphagia) taking conventional tablets.
- These limitations can be overcome by using powder-liquid 3-dimensional printing (3DP) to produce highly porous, rapidly disintegrating oral formulations, which can incorporate up to 1000 mg of active drug product per tablet, yet still rapidly disintegrate in the mouth when taken with a sip of liquid.
- The 3DP technology approach incorporates various taste-masking techniques and simply requires each unit dose to be taken with a small volume of liquid for ease of administration and swallowing.
- In the present study, the PK properties of a novel levetiracetam 3DP fast melt formulation (i.e., Spritam®) were compared to the reference listed product (i.e., Keppra®) including its behaviour following the administration of food. The safety and tolerability of the levetiracetam 3DP fast melt formulation were also evaluated.

METHODS

STUDY DESIGN
Single-center, randomized, open-label, single-dose, 3-period, 3-treatment, 3-sequence crossover study in healthy male and female subjects.

STUDY POPULATION
33 subjects: 19 male, 14 female; mean age 30 years old (range: 18-48); mean BMI 24.35 kg/m^2 (range:19–29); mostly of White ethnicity (27 subjects)

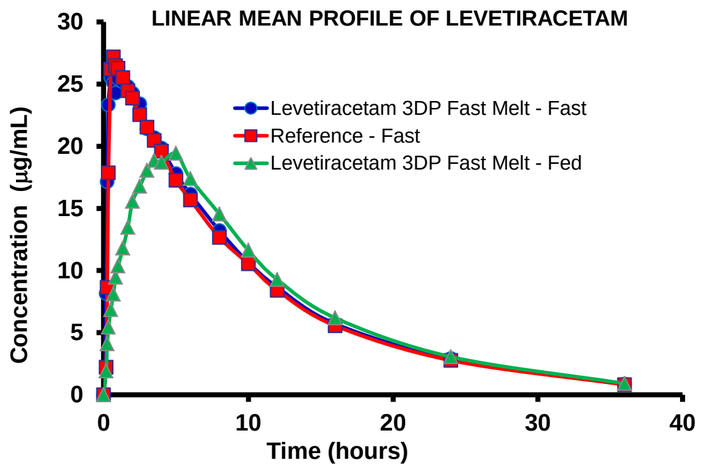
INVESTIGATIONAL PRODUCTS
Treatment-1: Levetiracetam 3DP fast melt 1000 mg formulation (i.e., Spritam®) taken under fasting conditions with a sip of water
Treatment-2: Keppra® 1000 mg film-coated tablets taken with 240 mL of water under fasting conditions
Treatment-3: Levetiracetam 3DP fast melt 1000 mg formulation (i.e., Spritam®) taken with a sip of water 30 minutes after a high-fat high-calorie breakfast

STUDY PLAN
- After an overnight fast of at least 10 hours, subjects were randomized to treatment.
- The volume of water and 3DP fast melt disintegration / swallowing time were recorded.
- On dosing day, blood samples were collected over 36 hours.
- Oral mucosal safety and local tolerability were assessed by monitoring erythema, edema or other adverse events (AEs).
- Subjects completed a product evaluation questionnaire on taste, mouth feel, and ease of administration within 5 minutes of swallowing each drug product and at the post study evaluation.
- Other safety assessments included laboratory tests, ECG, physical exam, vital signs, neurological function test and AEs.

BIOANALYTICAL AND STATISTICAL ANALYSIS
- HPLC with MS/MS detection was used for levetiracetam determination
- PK parameters were calculated using a non-compartmental approach (Phoenix® WinNonlin®, version 6.3).
- Statistical analysis of all PK parameters was based on an ANOVA model. Two-sided 90% CI of the ratio of geometric LSmeans from ln-transformed PK parameters were calculated.

RESULTS

LINEAR MEAN PROFILE OF LEVETIRACETAM



BIOEQUIVALENCE ASSESSMENT

PARAMETER	Ratio (Test/Ref) Fasted	90% Confidence Limits	
		Lower	Upper
lnC_{max}	106.45	99.74	113.62
lnAUC_{0-T}	102.94	100.93	105.00
ln$AUC_{0-\infty}$	102.78	100.72	104.89

3DP DISSOLUTION TIME

Elapsed Time Between the Sip of Water Consumed, 3DP Fast Melt Disintegration and Swallowing of the Medication

	3DP Fast Melt Fasted	3DP Fast Melt Fed[a]
N	32	32
Mean (SD) (secs)	11 (11)	11 (6)
Median (secs)	7.5	10.0

[a]The drug was administered 30 minutes after the start of the breakfast.

Total Volume of Water Consumed by Subjects

	3DP Fast Melt Fasted	3DP Fast Melt Fed[a]
N	32	32
Mean (SD) (mL)	12 (5)	14 (7)
Median (mL)	12.5	13.0

PHARMACOKINETIC ASSESSMENT

PARAMETER	3DP Fast Melt Fasted N=32		Reference Tablet Fasted N=32		3DP Fast Melt Fed N=31	
	Mean[a]	(c.v.%)	Mean[a]	(c.v.%)	Mean[a]	(c.v.%)
C_{max} (µg/mL)	33.273	(30.1)	30.480	(19.0)	20.481	(16.3)
AUC_{0-T} (µg·h/mL)	283.689	(20.0)	274.934	(18.2)	262.550	(15.1)
$AUC_{0-\infty}$ (µg·h/mL)	292.927	(19.9)	284.300	(18.0)	272.565	(15.2)
T_{max} (hours)	0.58	(73.7)	0.58	(69.9)	4.00	(21.6)
T_{half} (hours)	7.13	(13.3)	7.14	(16.3)	7.19	(15.3)

[a]Median for T_{max}.

GENDER SUBGROUP COMPARISONS

PARAMETER	Females				Males			
	3DP Fast Melt Fasted N=14		Reference Tablet Fasted N=14		3DP Fast Melt Fasted N=18		Reference Tablet Fasted N=18	
	Mean[a]	(c.v.%)	Mean[a]	(c.v.%)	Mean[a]	(c.v.%)	Mean[a]	(c.v.%)
C_{max} (µg/mL)	38.190	(22.4)	34.475	(13.6)	29.448	(32.5)	27.372	(16.7)
AUC_{0-T} (µg·h/mL)	323.946	(17.0)	304.702	(17.0)	252.379	(13.6)	251.780	(13.9)
$AUC_{0-\infty}$ (µg·h/mL)	331.870	(17.8)	312.097	(17.3)	262.639	(13.9)	262.679	(14.4)
T_{max} (hours)	1.00	(68.5)	0.67	(75.3)	0.50	(62.4)	0.50	(57.2)
T_{half} (hours)	6.47	(12.2)	6.34	(15.0)	7.641	(9.6)	7.77	(11.7)

[a]Median for T_{max}.

CONCLUSION

- A single 1000-mg oral dose of levetiracetam 3DP fast melt was safe and well tolerated.
- Most subjects agreed the mouth feel was acceptable and that the 3DP fast melt was easy to take and swallow.
- The majority indicated the 3DP fast melt disintegrated quickly in their mouth prior to swallowing, when taken with a small sip of water.
- The levetiracetam 3DP fast melt (i.e, Spritam®) is equivalent in rate and extent of absorption to the reference listed product (i.e., Keppra®) when given fasted.
- For the fed state, the extent of absorption of the levetiracetam 3DP fast melt was similar to the fasted state, but with a delay and a lower peak in the absorption.
- The effects observed during the fed state are unlikely to be of clinical significance with long-term administration, and may help to reduce the AEs and facilitate compliance.

Publication available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4875927/ Study funded by Aprecia Pharmaceuticals Company