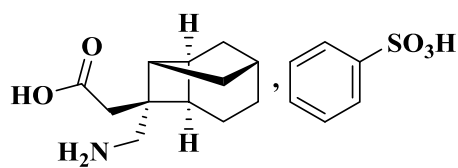


Crisugabalin Besilate Capsules

Benhuangsuan Kelijiabalin Jiaonang

2-[(1R,2R,3R,6R,8R)-2-(4-sulfamoylphenyl)-6-aminobicyclo[2.2.2]oct-5-yl]acetic acid [4.2.1.0<sup>3,8</sup>] -2- ]



$C_{12}H_{19}NO_2 \cdot C_6H_6O_3S$

367.46

20mg  $C_{12}H_{19}NO_2$

\_\_\_\_\_

|       |          |     |     |      |      |
|-------|----------|-----|-----|------|------|
|       |          |     |     | 20mg | 2    |
|       |          |     |     |      | ≥65  |
|       |          | 1   |     |      | 40mg |
| 2     |          |     |     | 20mg | 40mg |
|       |          |     |     |      | 2    |
| <hr/> |          |     |     |      |      |
|       |          |     |     | 1/2  | 1/4  |
| <hr/> |          |     |     |      |      |
|       |          | 65  |     |      |      |
|       |          |     | 65  |      |      |
|       |          |     |     |      | 585  |
|       |          |     | 327 |      |      |
|       | 457      |     | 6   |      | 274  |
|       | 12       |     |     |      |      |
| <hr/> |          |     |     |      |      |
|       |          |     |     | 178  |      |
| 40mg/ | 20mg bid | 180 |     |      |      |

≥1%  
40.4% 18.8%

|  | (          | ( %      |         |
|--|------------|----------|---------|
|  | d<br>4(. - | d<br>4(  | 4(. -   |
|  | 21(11.8)   | 42(23.3) | 7 (4.0) |
|  | 6 (3.4)    | 11 (6.1) | 1 (0.6) |
|  | 10 (5.6)   | 5 (2.8)  | 4 (2.3) |

|  | (SOC) |           | (%  |    |
|--|-------|-----------|-----|----|
|  | (PT)  |           | (%) |    |
|  |       | 82 (27.2) |     | 96 |
|  |       | 25 ( 8.3) |     | 27 |
|  |       | 9 (3.0)   |     | 11 |
|  |       | 6 (2.0)   |     | 6  |
|  |       | 3 (1.0)   |     | 3  |
|  |       | 8 (2.7)   |     | 9  |
|  |       | 3 (1.0)   |     | 3  |
|  |       | 5 (1.7)   |     | 5  |
|  |       | 4 (1.3)   |     | 4  |
|  |       | 3 (1.0)   |     | 3  |
|  |       | 4 (1.3)   |     | 4  |

0.7%

|          |     |       |          |       |
|----------|-----|-------|----------|-------|
|          |     | 123   |          | 40mg/ |
| 20mg bid | 122 | 80mg/ | 40mg bid | 3     |
|          | 1%  |       |          |       |
| 42.9%    |     | 29.0% |          |       |

| (%      |  |           |  |
|---------|--|-----------|--|
| d       |  | d         |  |
| 4()     |  | 4())      |  |
| ( %)    |  | ( %)      |  |
| 3 (2.4) |  | 9 (7.4)   |  |
| 5 (4.1) |  | 2 (1.6)   |  |
| 5 (4.1) |  | 29 (23.8) |  |
|         |  | 3 (2.4)   |  |

|  |         |          |         |
|--|---------|----------|---------|
|  | 4 (3.3) | 12 (9.8) | 0       |
|  | 4 (3.3) | 8 (6.6)  | 6 (4.8) |
|  | 4 (3.3) | 5 (4.1)  | 4 (3.2) |
|  | 3 (2.4) | 3 (2.5)  | 0       |
|  | 2 (1.6) | 4 (3.3)  | 0       |
|  | 0       | 5 (4.1)  | 0       |
|  | 1 (0.8) | 3 (2.5)  | 1 (0.8) |
|  | 3 (2.4) | 2 (1.6)  | 0       |
|  | 1 (0.8) | 3 (2.5)  | 0       |
|  | 3 (2.4) | 3 (2.5)  | 0       |

|      |       |          |    |       |
|------|-------|----------|----|-------|
|      |       | 2.0%     | 0% | 2     |
| 1    | 0.8%  | 40mg bid |    |       |
|      |       |          |    | /     |
|      | 22.7% | 5.7%     |    | 7.5%  |
| 0.3% | 79.5% |          |    | 20.5% |
|      | 5     |          | 3  |       |
|      |       |          |    | /     |

4.0% 1.6%  $\geq 7\%$  /

1.7% 0.8% /

1 0.6% 40mg bid

1.5% 0.3% /

6 2.0% 20mg bid 4 1.3% 40mg bid

3

2

/

18

252

65

eGFR $\geq$ 60 mL/min/1.73 m<sup>2</sup>

n=145

n=107

65

65

<65

n=448

$\geq$ 65

n=232

7.35 ~ 25.2%

CYP

CYP1A2 2B6 2C8 2C9 2C19 2D6 3A4

CYP1A

2 CYP2B6 CYP3A4

O

ATP1B1 OATP1B3 OATP2B1 OAT1 OATP1A2 MATE1 MATE2-K P-gp

BCRP

OAT3

OCT2

P-gp

BCRP

OATP1B1

OAT

P1B3 OATP2B1 OAT1 OATP1A2 MATE1 MATE2-K OAT3 OCT2

OAT3

OCT2

4-1

4-2

(

| PK                           | n=23       |    | n=23       |    | GMR<br>(90%CI)             |
|------------------------------|------------|----|------------|----|----------------------------|
|                              | Mean       | SD | Mean       | SD |                            |
| C <sub>max</sub> (ng/mL)     | 611 (173)  |    | 721 (162)  |    | 1.20<br>(111.26%, 128.48%) |
| AUC <sub>0-t</sub> (h*ng/mL) | 3190 (602) |    | 4570 (936) |    | 1.43<br>(138.31%, 148.10%) |
| AUC <sub>0-∞</sub> (h*ng/mL) | 3250 (601) |    | 4630 (931) |    | 1.42<br>(137.03%, 147.50%) |

)

| PK                           | n=24       |    | n=24        |    | GMR<br>(90%CI)             |
|------------------------------|------------|----|-------------|----|----------------------------|
|                              | Mean       | SD | Mean        | SD |                            |
| C <sub>max</sub> (ng/mL)     | 617 (154)  |    | 687 (166)   |    | 1.12<br>(104.23%, 119.45%) |
| AUC <sub>0-t</sub> (h*ng/mL) | 3520 (758) |    | 5680 (1100) |    | 1.62<br>(156.66%, 167.45%) |
| AUC <sub>0-∞</sub> (h*ng/mL) | 3570 (762) |    | 5730 (1100) |    | 1.61<br>(155.91%, 166.79%) |

5

| PK                                | n=21        |    | n=21        |    | GMR<br>(90%CI)     |
|-----------------------------------|-------------|----|-------------|----|--------------------|
|                                   | Mean        | SD | Mean        | SD |                    |
| C <sub>max,ss</sub> (ng/mL)       | 1320 (308)  |    | 1070 (269)  |    | 0.81<br>(76%, 87%) |
| AUC <sub>0-tau,ss</sub> (h*ng/mL) | 7350 (1100) |    | 6190 (1430) |    | 1.12<br>(79%, 87%) |

:C<sub>max,ss</sub>

AUC<sub>0-tau,ss</sub>

0

-

\_\_\_\_\_ 5~120 mg  
 1.33~1.67h  
 h AUC<sub>0-t</sub> T<sub>max</sub> 3.96 h v.s. 1.37  
 C<sub>max</sub> 33.96%

0.9 400 2000 10000 ng/mL  
 2.7% 2.8% 3.3%  
 5~120 mg V<sub>z</sub>/F 67~133L

CYP450

CYP CYP1A2 2B6 2C8 2C9 2C19 2D6 3A4  
 CYP1A2 CYP2B6 CYP3A4  
 OATP1B1 OATP1B3 OATP2B1 OAT1 OATP1A2 MATE1 MATE2-  
 K P-gp BCRP OAT3 OCT2

2%  
 5~120mg CL/F 10.6~13.8L/hr  
 3.68~6.42 h

|                  |                                        |                    |
|------------------|----------------------------------------|--------------------|
|                  | 40mg                                   | 79.21%             |
| 6.55%            |                                        |                    |
|                  |                                        | n=606              |
|                  | n=74                                   | 6.57~10.1%         |
|                  | 20 mg                                  | 90≤GFR<130 mL/min, |
| n=8              | 60≤GFR<90 mL/min, n=8                  | 30≤GFR<60 mL/min   |
| n=8              | 15≤GFR<30 mL/min, n=8                  |                    |
| C <sub>max</sub> | 6.00% 13.83% 21.63% AUC <sub>0-∞</sub> | 14.63% 119.57%     |
| 272.61%          |                                        |                    |

1/2 1/4

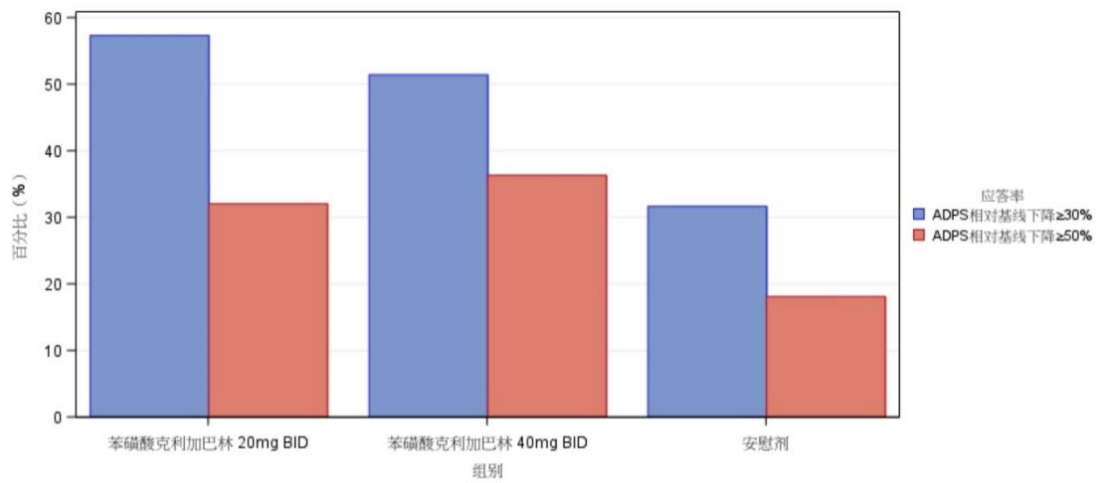
PK

PK

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|     |                                     |    |
|-----|-------------------------------------|----|
|     | 18-75                               |    |
| ≥6  | HbA1c ≤ 9.0%                        | 30 |
| VAS | ≥ 40 mm < 90 mm                     |    |
|     | 20mg bid 40mg bid 60mg bid 80mg bid |    |

|     |          |          |          |               |               |               |       |          |
|-----|----------|----------|----------|---------------|---------------|---------------|-------|----------|
|     | 300mg/   |          |          |               |               |               |       | 13       |
|     | 20mg bid | 40mg bid |          |               |               |               |       |          |
|     |          |          |          |               |               |               | 1:1:1 |          |
|     | 20mg bid | 40mg bid |          |               |               |               |       | 13       |
|     |          |          | 13       | ADPS          |               |               |       |          |
|     |          | 20mg bid | 40mg bid |               |               |               | 13    | ADPS     |
|     |          |          |          | -2.24 (1.550) | -2.16 (1.785) | -1.23 (1.681) |       |          |
| 13  | ADPS     |          | ≥30%     |               |               |               | 102   | 57.3% 92 |
|     | 51.4%    | 56       | 31.6%    | 13            | ADPS          |               | ≥50%  |          |
|     | 57       | 32.0%    | 65       | 36.3%         | 32            | 18.1%         | 40mg/ | 20mg     |
| bid | 80mg/    | 40mg bid |          |               | p<0.0001      |               | 1     | 2        |
|     |          | 13       | DSIS     |               |               | VAS           |       |          |



2 13 ADPS

52 40mg bid  
40mg bid  
20mg bid  
52 VAS  
301 43  
52 VAS -23.4 $\pm$ 19.38 2-  
52 VAS

18 1 VAS  $\geq 40$  mm

1:1:1 20mg bid 40mg bid  
12 12 ADPS  
20mg bid 40mg bid  
12 ADPS -2.338 (1.6615)  
-2.513 (2.0055) -1.047 (2.0308) 40mg bid ADPS  
95% CI -1.498 -1.983 -1.013 p<0.001 20mg bid  
ADPS 95% CI -1.140 -1.631 -0.649

3

40mg bid

ADPS

30%

61.2%

66

44

(35.5%)

12

ADPS

50%

(37.2%)

46 (38.0%)

25 (20.2%)

4

12

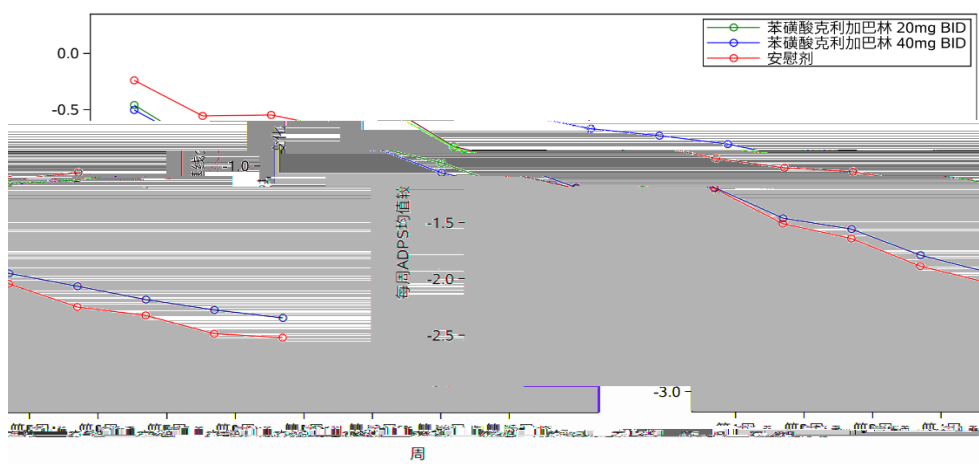
14

80mg/ 40mg bid

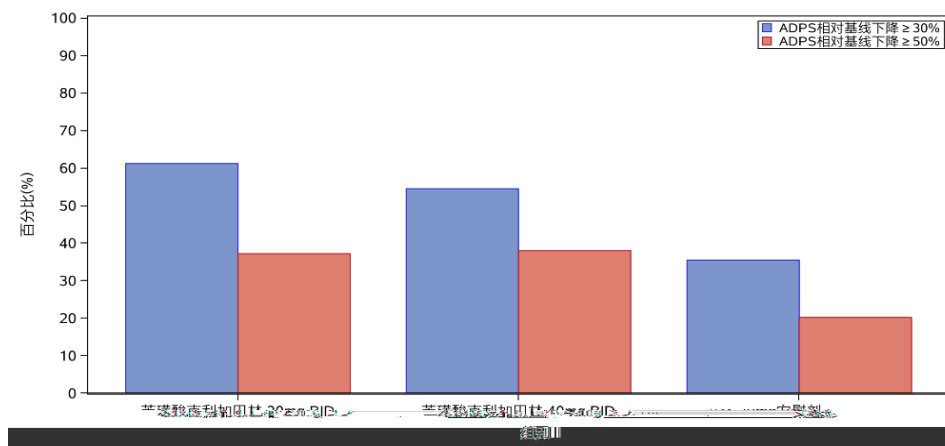
264 71.0%

26 VAS

-39.09    19.590



3 ADPS



4 12 ADPS

| γ-                 | GABA           | GABA <sub>A</sub> GABA <sub>B</sub> |           |
|--------------------|----------------|-------------------------------------|-----------|
|                    |                | [ <sup>3</sup> H]                   |           |
|                    | Ames           | CHL                                 |           |
|                    |                |                                     | 4         |
|                    | 2              | 7                                   | 15 60     |
| 240mg/kg/ [        |                | MRHD                                | 80mg/ 1.8 |
| 7.3 29 ] 240mg/kg/ |                |                                     |           |
|                    |                | 240mg/kg/                           |           |
|                    | 60 mg/kg/      | 240mg/kg/                           |           |
| -                  |                |                                     | 6~17      |
|                    | 5 20 100mg/kg/ | 100 mg/kg/                          |           |
|                    |                | -                                   | 100mg/kg/ |
| AUC                | MRHD           | 37                                  |           |
| -                  |                |                                     | 6~18      |
|                    | 5 20 80mg/kg/  | 80mg/kg/                            | -         |
|                    |                |                                     | -         |
|                    | 20mg/kg/       | AUC                                 | MRHD 3.4  |
|                    |                | 6                                   | 21        |
|                    | 5 20 100mg/kg/ | 100 mg/kg/                          |           |
|                    |                | 20mg/kg/                            | AUC       |
| MRHD 5.2           |                | 100 mg/kg/                          | AUC       |
| MRHD 33            |                |                                     |           |

SD 104 20 60  
200 mg/kg/ 200mg/kg/ MRHD 101  
140 AUC rasH2 26  
6 100 400 1500 mg/kg/  
1500 mg/kg/ MRHD 216 265  
AUC

25

/ /

9 / 6

/

24

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