

|      |    |    |
|------|----|----|
| 2008 | 09 | 28 |
| 2009 | 03 | 13 |
| 2010 | 05 | 31 |
| 2011 | 11 | 28 |
| 2011 | 12 | 08 |
| 2012 | 06 | 07 |
| 2013 | 03 | 14 |
| 2013 | 05 | 22 |
| 2013 | 12 | 05 |
| 2014 | 05 | 18 |
| 2015 | 12 | 24 |
| 2016 | 11 | 01 |
| 2017 | 02 | 24 |
| 2017 | 08 | 28 |
| 2017 | 09 | 25 |
| 2018 | 03 | 13 |
| 2018 | 10 | 10 |
| 2019 | 05 | 29 |
| 2019 | 06 | 27 |
| 2020 | 06 | 22 |
| 2020 | 06 | 28 |

### 警示语

#### 会增高痴呆相关性精神病老年患者的死亡率

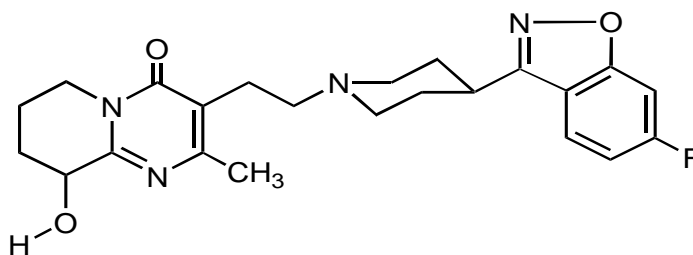
与安慰剂相比，使用非典型性抗精神病药物治疗患有痴呆相关性精神病的老年患者时，死亡的风险会增加。对在患有痴呆相关性精神病的老年患者中进行的17项安慰剂对照临床试验（平均众数治疗时间为10周）的分析显示，药物治疗组患者死亡的危险性为安慰剂对照组的1.6 - 1.7倍。在一项典型的10周对照试验中，药物治疗组的死亡率为4.5%，安慰剂对照组为2.6%。虽然死亡原因各异，但大多数死于心血管病（如心衰、猝死）或感染（如肺炎）。本品未被批准用于治疗痴呆相关性精神病患者（参见【注意事项】）。

®

Paliperidone Extended-Release Tablets

Palipaitong Huanshi Pian

± -3-[2-[4-(6- -1,2- -3- )-1- ] ]-6,7,8,9- -9- -2-  
-4H- [1,2-*a*] -4-



C<sub>23</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>3</sub>

426.49

200K

K29-32

200K

K29-32

7000K

K29-32

3350

398-10

3350

HPMC 2910 6 cP

HPMC 2910 15 cP

400

HPMC 2910 6 cP

3 mg/

6 mg/

9 mg/

12-17

≥29Kg

3 mg 6 mg 9 mg

—

6 mg

6 mg

12 mg/

3 mg/

5

6 mg/

3 mg/

12 mg/

6

**12-17**

12-17

≥29Kg

3 mg

3 mg/

5

51 kg

6 mg

51 kg

12 mg

|       |       |      |         |
|-------|-------|------|---------|
|       |       |      |         |
| 51Kg> | ≥29Kg | 3mg/ | 3-6mg/  |
|       | ≥51Kg | 3mg/ | 3-12mg/ |
|       |       |      | 6mg/    |
|       |       |      | 12mg/   |

|            |            |      |           |
|------------|------------|------|-----------|
| 50 mL/min  | <80 mL/min | 3 mg |           |
|            | 6 mg       |      | 10 mL/min |
| <50 mL/min |            | 3 mg | 3 mg      |
|            | <10 mL/min |      |           |
|            | Child-Pugh | A    | B         |

|      |           |            |            |
|------|-----------|------------|------------|
|      | 10 mL/min | <50 mL/min | 3 mg       |
| 3 mg |           |            | <10 mL/min |

<12

- 
- 
- 
- QT
- 
- 
- 
- 
-

- 
- 
- 
- 
- 
- 
- 
- 
- 
- 

TTP

5%

2%

6

1205

850

3 mg~12 mg

3 mg~15 mg n=104

MedDRA

—

ADRs

/

QT

1

6

≥2%

1

6

2%

|   | 3 mg<br>1  | 6mg<br>1   | 9 mg<br>1  | 12 mg<br>1 |            |
|---|------------|------------|------------|------------|------------|
| / | N=127<br>% | N=235<br>% | N=246<br>% | N=242<br>% | N=355<br>% |
|   | 11         | 12         | 14         | 14         | 12         |
|   | 6          | 5          | 4          | 5          | 4          |
|   | 5          | 2          | 7          | 7          | 2          |
|   | 5          | 3          | 7          | 5          | 3          |
|   | 4          | 3          | 8          | 10         | 4          |
|   | 3          | 3          | 4          | 3          | 3          |
|   | 2          | 1          | 4          | 3          | 1          |
|   | 1          | 1          | 4          | 4          | 1          |
|   | 1          | 5          | 3          | 6          | 4          |
|   | 0          | <1         | 2          | 1          | 0          |
|   | 0          | 0          | 2          | 0          | 0          |
|   | 9          | 4          | 4          | 7          | 4          |
|   | 2          | 7          | 7          | 7          | 3          |
|   | 3          | 1          | 3          | <1         | 2          |
|   | 2          | 1          | 1          | <1         | 0          |
|   | 2          | 0          | 2          | 1          | 1          |
|   | 2          | 1          | 2          | 4          | 1          |
|   | 2          | 3          | 4          | 5          | 5          |
|   | 2          | 3          | 1          | 3          | 1          |
|   | 1          | 3          | 2          | 2          | 1          |
|   | 0          | <1         | 1          | 4          | <1         |
|   | 2          | <1         | 2          | 2          | 1          |
|   | 2          | 1          | 2          | 2          | 1          |

12 12

2

12

12

N = 545

ADRs

/  
 $\geq 1/10$

2

$\geq 1/100$  <1/10

$\geq 2\%$

12-17

2

2%

|   | 1.5 mg<br>1 | 3 mg<br>1 | 6 mg<br>1 | 12 mg<br>1 |      |
|---|-------------|-----------|-----------|------------|------|
| / | N=54        | N=16      | N=45      | N=35       | N=51 |
|   | 4           | 0         | 4         | 0          | 2    |
|   | 9           | 6         | 7         | 14         | 22   |
|   | 0           | 0         | 2         | 9          | 4    |
|   | 6           | 13        | 13        | 26         | 2    |
|   | 4           | 6         | 11        | 17         | 0    |
|   | 9           | 6         | 4         | 14         | 4    |
|   | 2           | 6         | 7         | 11         | 0    |
|   | 2           | 0         | 4         | 9          | 0    |
|   | 0           | 0         | 0         | 11         | 0    |
|   | 2           | 6         | 2         | 3          | 0    |
|   | 2           | 6         | 2         | 3          | 0    |
|   | 4           | 0         | 2         | 0          | 2    |
|   | 0           | 0         | 4         | 0          | 0    |
|   | 0           | 6         | 0         | 0          | 0    |
|   | 0           | 0         | 0         | 3          | 0    |
|   | 0           | 0         | 0         | 3          | 0    |
|   | 0           | 0         | 0         | 3          | 0    |
|   | 0           | 0         | 4         | 3          | 0    |
|   | 0           | 0         | 0         | 3          | 0    |
|   | 0           | 6         | 7         | 6          | 0    |
|   | 0           | 0         | 2         | 0          | 0    |
|   | 0           | 0         | 2         | 0          | 0    |
|   | 0           | 6         | 11        | 3          | 10   |
|   | 0           | 0         | 2         | 9          | 12   |
|   | 2           | 6         | 2         | 0          | 0    |

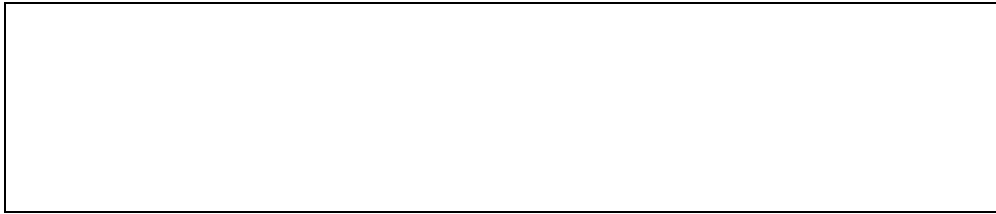
|  |   |   |   |   |   |
|--|---|---|---|---|---|
|  | 2 | 0 | 2 | 0 | 2 |
|  | 0 | 0 | 0 | 3 | 2 |
|  | 0 | 0 | 0 | 3 | 0 |
|  | 0 | 0 | 2 | 3 | 0 |
|  | 0 | 0 | 0 | 3 | 0 |
|  | 0 | 0 | 2 | 0 | 0 |
|  | 0 | 0 | 4 | 0 | 0 |
|  | 0 | 6 | 0 | 0 | 0 |
|  | 0 | 0 | 0 | 3 | 0 |
|  | 4 | 0 | 2 | 3 | 0 |
|  | 0 | 0 | 2 | 3 | 0 |
|  | 7 | 6 | 2 | 3 | 0 |

6  
3% 1%  
2% 0%  
6  
<1%  
6 2%  
12 mg 9 mg  
6  
2%  
6  
**EPS**  
-

/



|               |                  |        |               |     |   |      |       |
|---------------|------------------|--------|---------------|-----|---|------|-------|
|               | 6                |        |               |     |   | EPS  |       |
|               | EPS              | 1      | Simpson-Angus |     |   |      |       |
|               | 2                | Barnes |               |     |   |      |       |
|               | 3                |        |               | EPS | 3 | 4    | EPS   |
| Simpson-Angus |                  |        | EPS           |     |   | 9 mg | 12 mg |
|               |                  |        | EPS           |     |   | 3 mg | 6 mg  |
|               | #uÍF4b7\Ô`#r7^uİ |        |               |     |   |      | 4     |



EPS

5

5 MedDRA

EPS

—

|            |    | 1.5 mg       | 3 mg        | 6 mg        | 12 mg       |             |
|------------|----|--------------|-------------|-------------|-------------|-------------|
| <b>EPS</b> |    | <b>N=51)</b> | <b>N=54</b> | <b>N=16</b> | <b>N=45</b> | <b>N=35</b> |
| EPS        | AE | 0            | 6           | 25          | 22          | 40          |
|            |    | 0            | 4           | 6           | 11          | 17          |
|            |    | 0            | 2           | 0           | 11          | 14          |
|            |    | 0            | 2           | 6           | 7           | 11          |
|            |    | 0            | 0           | 6           | 2           | 14          |
|            |    | 0            | 2           | 6           | 2           | 6           |

6

C

HDL LDL

6

≥ 7%

3 mg 6 mg

7% 6%

5%

9 mg

12 mg 9% 9%

6a            9            8            1

/

/

≥2%

**6a            9            8            1**

/

|                                      |
|--------------------------------------|
| /                                    |
| *<br><br>*            *            * |
| *                                    |

6b            9            8            1

/

<2%

**6b            9            8            1**

/  
<2%

| /             |
|---------------|
| * *<br><br>QT |

$\gamma$ -

\*

\*

\*

6c

/

9

8

1

6c

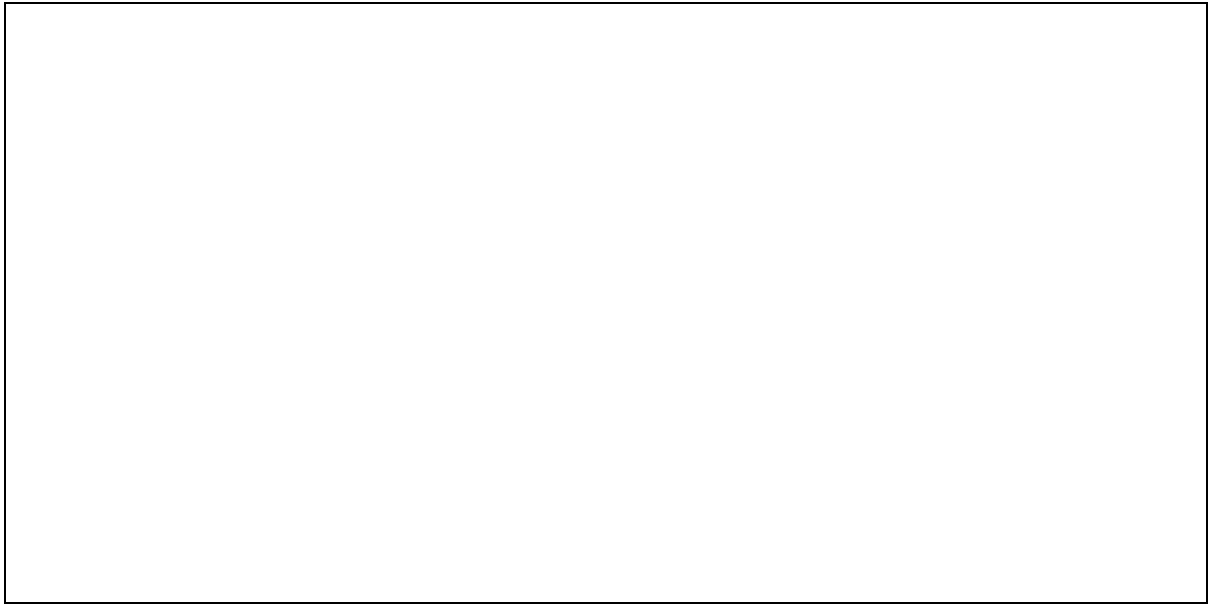
/

9

8

1

|   |
|---|
| / |
|   |



14

6

14

7

$\geq 10\%$

1% 10%

0.1% 1%

0.01% 0.1%

$< 0.01\%$

7 8





Stevens-Johnson /



\*

Stevens-Johnson /

|    |       |
|----|-------|
| *  | 0.05% |
| 0% | 0.14% |

NMS NMS

EPS

NMS

1

2

3

NMS

NMS

NMS

QT

QT QTc

QTc

1A

III

|       |                                |                   |          |                |       |       |
|-------|--------------------------------|-------------------|----------|----------------|-------|-------|
|       |                                | QTc               |          |                | QT    |       |
|       |                                |                   | QTc      |                |       | /     |
|       | 1                              |                   | 2        |                | 3     | QTc   |
| 4     |                                | QT                |          |                |       |       |
|       | 400 mg                         |                   | QT       |                | QT    |       |
|       |                                |                   |          |                | 6     |       |
| QT    | n = 141                        | 8 mg              |          |                | n=50  | 8     |
| QTcLD |                                |                   | 12.3msec | 90%CI:8.9;15.6 | 8 mg  | 1.5   |
|       |                                |                   | 12 mg    |                |       |       |
|       | C <sub>max</sub> ss            | 113 ng/mL         | 45 ng/mL |                | 4 mg  |       |
|       | C <sub>max</sub> ss = 35 ng/mL |                   | 2        | 1.5            | QTcLD |       |
|       | 6.8msec                        | 90% CI: 3.6; 10.1 |          |                |       | 60 ms |
| QTcLD | 500 ms                         |                   |          |                |       |       |
|       |                                |                   |          | ECG            |       | 12    |
| mg    |                                | 6                 |          | 60 ms          |       | 62 ms |
|       |                                |                   | QTcLD    | 500 ms         |       |       |

**9a**

12-17

**12-17**

6

**6**

9a



6 6 182  
 12-17  
 6 ≥7% 10  
 10 12-17 6

|    |     | 1.5 mg/<br>n=51 | 3 mg/<br>n=54 | 6 mg/<br>n=16 | 12 mg/<br>n=45 | 12 mg/<br>n=34 |
|----|-----|-----------------|---------------|---------------|----------------|----------------|
| kg | 0.0 | 0.3             | 0.8           | 1.2           | 1.5            |                |
|    | 2%  | 6%              | 19%           | 7%            | 18%            |                |

33% ≥7%

182

0.1 4%

D<sub>2</sub>

GnRH





6  
3 mg, 6 mg, 9 mg, 12 mg  
0.25%  
0.22%  
65

$\alpha$

**TTP**

TTP

TTP

$\alpha$ 1a

$\alpha_1 a$

$\alpha_1$

/

Claims

=1.26 95% CI 1.02-1.56

20-34

/

9-

9-

9-

<12

114

≥65

21

≥75

6

3 mg~12 mg

≥65

6

3 mg~15 mg  
n = 1796

|     |      |     |    |      |     |
|-----|------|-----|----|------|-----|
| 125 | 7.0% | ≥65 | 22 | 1.2% | ≥75 |
|-----|------|-----|----|------|-----|

CYP450

|        |        |        |             |        |        |        |
|--------|--------|--------|-------------|--------|--------|--------|
| CYP450 | CYP1A2 | CYP2A6 | CYP2C8/9/10 | CYP2D6 | CYP2E1 | CYP3A4 |
| CYP3A5 |        |        |             |        |        |        |

P-

P-

12mg

500mg

2000mg

CYP1A2 CYP2A6 CYP2C9 CYP2C19

CYP2D6 CYP3A4

P-gp

CYP2D6

3 mg

20 mg/

CYP2D6

CYP2D6 16% 90% CI: 4, 30  
200 mg C<sub>max</sub>  
AUC 37% P-gp  
35%  
CYP  
12 mg 2 500 mg/  
C<sub>max</sub> AUC 50%

405 mg  
QT

QT

$\alpha$

|            |          | $\beta$ |   | /          |  | $\alpha$  |         |
|------------|----------|---------|---|------------|--|-----------|---------|
|            | DSM-IV   | 6       |   | 37         |  |           |         |
|            |          |         |   | 3 mg-15 mg |  |           |         |
| 9 mg/      | 12 mg/   | 15 mg/  |   |            |  | 3 mg/     | 6 mg/   |
|            | PANSS    | PANSS   |   | PANSS      |  | /         | /       |
|            |          | PSP     |   | PSP        |  |           |         |
| 3          | n = 1665 |         |   | PANSS      |  |           |         |
| PSP        |          |         |   | 65         |  |           |         |
|            |          | DSM-IV  |   | PANSS      |  | $\leq 70$ |         |
| PANSS      | $\leq 4$ | 8       |   |            |  |           |         |
|            | 6        |         |   | 3-15mg     |  | 1         |         |
|            |          |         |   | PANSS      |  | PANSS     |         |
|            |          |         | 6 |            |  |           |         |
| 1.5-12 mg/ |          |         |   |            |  |           | N = 149 |
| N = 51     |          | 12-17   |   | DSM-       |  |           | PANSS   |

11 **R076477-PSZ-3001** 6

3 mg 6 mg 12 mg

**LOCF**

|              | N=51         | 1.5 mg<br>N=54 | 3 6 mg*<br>N=48 | 6 12 mg**<br>N=47 |
|--------------|--------------|----------------|-----------------|-------------------|
| <b>PANSS</b> |              |                |                 |                   |
| (SD)         | 90.6 (12.13) | 91.6 (12.54)   | 90.6 (14.01)    | 91.5 (13.86)      |
| (SD)         | -7.9 (20.15) | -9.8 (16.31)   | -17.3 (14.33)   | -13.8 (15.74)     |
| P- (vs )     |              | 0.508          | 0.006           | 0.086             |
| (SE)         |              | -2.1 (3.17)    | -10.1 (3.27)    | -6.6 (3.29)       |
| n (%)        | 17 (33.3)    | 21 (38.9)      | 31 (64.6)       | 24 (51.1)         |
| n (%)        | 34 (66.7)    | 33 (61.1)      | 17 (35.4)       | 23 (48.9)         |
| P (vs )      |              | 0.479          | 0.001           | 0.043             |

PANSS  $\geq 20\%$

LOCF =

\* < 51 kg 3 mg  $\geq 51$  kg 6 mg

\*\* < 51 kg 6 mg  $\geq 51$  kg 12 mg

8 18

$\geq 12$

N = 112

N = 114

3 mg/

9 mg/

8

26

PANSS

26 PANSS

$\geq 20\%$

12 **R076477-PSZ-3003** 26

**LOCF**

|              | 3-9 mg<br>N=112 | 5-15 mg<br>N=114 |
|--------------|-----------------|------------------|
| <b>PANSS</b> |                 |                  |
| <b>8</b>     | 89.6 (12.22)    | 92.0 (12.09)     |
| (SD)         | -19.3 (13.80)   | -19.8 (14.56)    |
| (SD)         | 0.935           |                  |
| P- (vs )     | 0.1 (1.83)      |                  |
| (SE)         |                 |                  |



|   |   |                               |
|---|---|-------------------------------|
| <b>PANSS</b><br><b>26</b><br>(SD)<br>(SD)<br>P- (vs )<br>(SE) | 89.6 (12.22)<br>-25.6 (16.88)<br>0.877<br>-0.3 (2.20) | 92.0 (12.09)<br>-26.8 (18.82) |
| <b>26</b><br>n (%)<br>n (%)<br>P- (vs )                       | 86 (76.8)<br>26 (23.2)<br>0.444                       | 93 (81.6)<br>21 (18.4)        |

PANSS  $\geq 20\%$

LOCF =

2 D<sub>2</sub> 5- 2 5HT<sub>2A</sub>  
1 2 H<sub>1</sub>  
1 2  
+ - - -  
Ames  
2.5 mg/kg/  
0.63 mg/kg mg/m<sup>2</sup>  
2.5 mg/kg/  
Beagle  
0.31~5.0 mg/kg  
10 mg/kg/ 5 mg/kg/  
mg/m<sup>2</sup> 8  
mg/m<sup>2</sup>

|                   | Swiss albino |                           |             | Wistar |      |
|-------------------|--------------|---------------------------|-------------|--------|------|
|                   | 0.63         | 2.5                       | 10 mg/kg    |        | 18   |
| mg/m <sup>2</sup> |              |                           |             |        |      |
| D <sub>2</sub>    |              |                           |             |        |      |
| AUC               | 24           | 73                        |             |        |      |
|                   |              | 0.63 mg/kg/<br>2.5 mg/kg/ |             |        |      |
|                   |              |                           | 2~3         |        |      |
|                   |              |                           | 40          |        | 0.31 |
| 1.25 5 mg/kg/     |              |                           | 0.31 mg/kg/ |        | +    |
| AUC               |              |                           |             |        |      |
|                   |              |                           | 12          |        |      |
| C <sub>max</sub>  |              |                           |             |        |      |
|                   |              | 3mg-12 mg                 |             |        |      |
|                   |              | 23                        |             |        |      |
|                   |              | 4-5                       |             |        |      |
|                   | 1.7          | 1.2-3.1                   |             |        |      |
|                   |              |                           | 9 mg        |        |      |
|                   | 12mg         | 1                         |             |        |      |
|                   |              |                           | 4mg         |        |      |
|                   |              | 38%                       | 125%        |        | 1    |



10%

CYP2D6

3 mg

CrCl = 50 mL/min < 80 mL/min

32%

CrCl = 30 mL/min < 50 mL/min 64%

CrCl = 10 mL/min < 30 mL/min 71%

AUC<sub>inf</sub>

1.5 2.6 4.8

24

,40

51

23

CrCl ≥ 80 mL/min

Child-Pugh B

12-17

29Kg

<51 kg <112 lbs

≥51 kg ≥112 lbs

23%

CYP1A2

15-30

/ /  
7 / 28 /

24

JX20100237

3mg: H20160549

6mg: H20160550

9mg: H20160551

3mg: J20170010

6mg: J20170011

9mg: J20170012

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