

2006	03	23
2007	03	22
2007	04	06
2011	07	14
2013	09	18
2015	05	15
2016	11	16
2017	01	18
2018	08	08
2020	06	24
2020	08	28
2021	01	29
2022	01	20

ALT	AST	11%	ULN	3
		1		
			>12	
1		>20		
	1			
			>3xULN	
			≥2xULN	

1 2
Copper T380A IUD LNg20 IUS

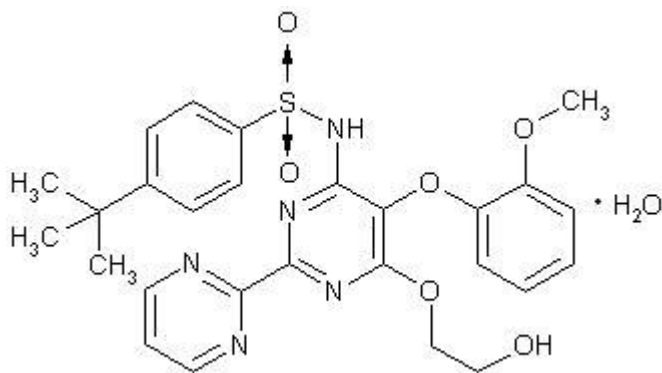
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® Tracleer®

Bosentan Tablets

Boshengtian Pian

4- -N-[6- 2- - -5- 2- - -[2,2'] -4-]-



$C_{27}H_{29}N_5O_6S \cdot H_2O$

569.64

	WHO	II -IV	PAH	WHO	1
				WHO	
II -IV		PAH 60%		PAH 21%	
		PAH 18%			
WHO	II				
		WHO	II		

(1) 62.5mg C₂₇H₂₉N₅O₆S

(2) 125mg C₂₇H₂₉N₅O₆S

		2	62.5mg	4
125mg	2	2	125mg	

3

≥2

1

3

ALT/AST

> 3 ≤5×ULN

2

> 5 ≤8×ULN

2

> 8 × ULN

3

2

2	40kg 12	18	12			62.5mg
	1	1	10			62.5mg
				36	1	10
	62.5mg				1	
3~7						
20						2486
45		100 mg – 2000mg	1838	1%		0.5%
		11.5%	/		13.2%	
10.9%	/	9.9%				
		20		/		
$\geq 1/10$		$\geq 1/100$	$< 1/10$	$\geq 1/1,000$	$< 1/100$	$\geq 1/10,000$
$< 1/1,000$		$< 1/10,000$				
2		20				

		1
		1
		1
		2
		/ 1
		3
		1,4
		1
		1,4
		1,4
		1
		/ 1
		1
		5

1
2
3
4
5

9.9% 9.1%
11.5% 9.8%
13.2% 10.9%

3~15] 2 mg/kg
BREATHE-3
16%

BREATHE-3 n=19
12
21%

10 [PAH

	PAH						, 100	
32mg	FUTURE 1/2, FUTURE 3/					2mg/kg	n=33	2mg/kg
	n=31		4mg/kg		n=36	6	3	1
15	1	2	79	2	12	71.8	0.4-258	

	PAH						69.0% vs 41.3%
	PAH					71.8	
17.4						25%	
	20%		17%		15%	13%	10%
	10%			2			10%
21	2			6	3	1	/
				9%	5%		

	PPHN					FUTURE-4	13
	2 mg/kg					8	
			4.5		0.5-10	4.0	2.5-6.5
							7
	3	0		2	0		2

26

	20					
	≥3			11.2%	2.4%	≥8
3.6%	0.4%					≥2
				0.2%	5	0.3%
						6

	FUTURE 1/2	FUTURE 3/	100	PAH
	2%		≥3 x ULN	
	FUTURE-4	13	PPHN	2mg/kg
10	0.5-10.0		≥3 x ULN	
	3			

	10 g/dL		8.0%	3.9%
	FUTURE 1/2	FUTURE 3/	100	PAH
10.0%			10 g/dL	8 g/dL

FUTURE-4

13 PPHN

6

•

•

2

•

/

(AST) /

ALT
2

3 (ULN)

•

A

•

AST
26

ALT

A

12

1

20

≥2

AST / ALT 3xULN
2xULN

PAH 1.7%

4-12

1 3

3

“ ”

85mm Hg

62.5mg

4	125mg		5					
25	WHO	III	IV	PAH	23			2
					3	6	25%	
	50%	6	22					
		1		3			6	2
				2				

	CYP3A4	CYP2C9	
125mg	2	$\geq 60 \text{ mg/kg/}$	mg/m^2
	-1		-
			1500 mg/kg/

65	65
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P ₄₅₀			
P ₄₅₀	CYP2C9	CYP3A4	CYP3A4
		CYP2C9	

Confidential - FOIA Exemptions Apply in U.S.

	BREATHE-1				AC-052-351			
	125mg b.i.d.		n=69		125mg b.i.d.		n=11	
	n=74				n=21			
[n(%)]	5	7% ^a	14	20%	0	0% ^b	3	27%
	1	1%	2	3%	0	0%	0	0%
PAH	3	4%	9	13%	0	0%	3	27%
PAH	3	4%	6	9%	0	0%	3	27%
^c	2	3%	3	4%	0	0%	3	27%

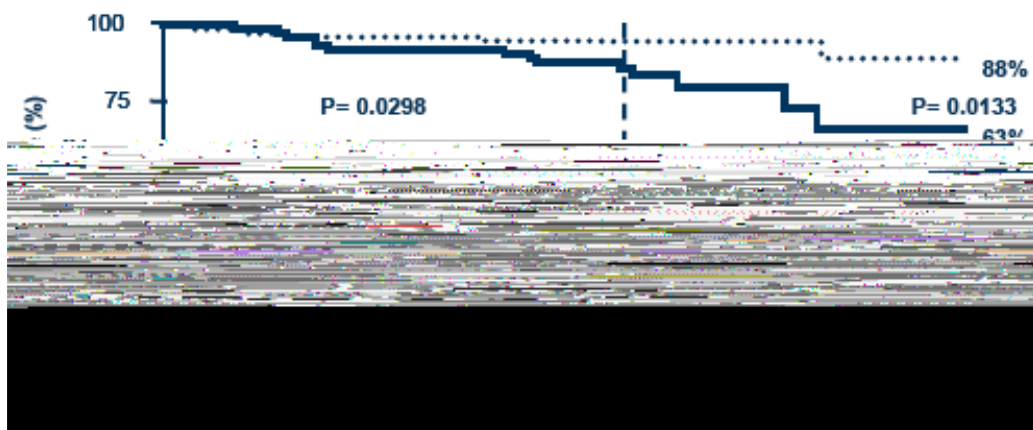
^a Log-rank p=0.015

^b Fish p=0.033

^c

* PAH

1 BREATHE-1 28



BREATHE-1

Kaplan-Meier

n=74 n=69 16
n=19 n=13 28

	C _{max}	t _{1/2}	AUC _{0-∞}
14 125mg	2286ng/ml	2.3	8912ng.hr/ml
	1234 3337	1.0-6.0	6296 11531

125mg b.i.d.	95%	t _{max}	
	2		
	50%		3-5
		2	
	18L	8L/h	>98%
	P ₄₅₀	CYP3A4	CYP2C9
		Ro 48-5033	
			25%
		t _{1/2}	5.4
31.25mg	62.5mg	125mg	2
			AUC CV%
3496	49	5428	79
		6124	27
		ng.h/mL	125mg b.i.d.
AUC		8149	47
		ng.h/mL	10 – 20 kg
			20 – 40kg
			> 40kg
		43%	67%
		75%	
		65	
	Child-Pugh	A	
	AUC	9%	Ro 48-5033
AUC	33%		
	Child-Pugh B		Ro
48-5033	5	Child-Pugh B	
	3		Child-Pugh B
	AUC	[95% CI]	360 [212-613] ng.h/mL
4.7	AUC	[95% CI]	76.1 [9.07-638] ng.h/mL
			Ro 48-5033
AUC	[95% CI]	106 [58.4-192] ng.h/mL	12.4
			Ro 48-5033
AUC	[95% CI]	8.57 [1.28-57.2] ng.h/mL	
	Child-Pugh B		Ro 48-
5033			
	Child-Pugh C		
	Child-Pugh B	C	

30mL/min
3%

10%

2

, 15-30

56 /

48

JX20160194

62.5mg HJ20110291

125mg HJ20170013

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