R

2020 06 02
2021 09 26
2021 11 29
2023 05 12

Afatinib Dimaleate Tablets

Malaisuan Afatini Pian

(2E)-N-[4-(3- -4-)-7-[[(3S)- -3-]] -6-]-4-
( ) -2-

1. EGFR

(NSCLC) EGFR TKI

2.

(NSCLC)

_____ $C_{24}H_{25}ClFN_5O_3$ 1 20mg 2 30mg 3 40mg

d 20mg/

ILD

ILD

[ ]

1

8

<30mL/min

Child Pugh A Child Pugh B

Child Pugh C

P- P-gp

P- (P-gp) P-gp

P-gp

6 P-gp 12 P-gp

P-gp

10mg P gp

P- P-gp

P-gp

10mg P-gp 2-3

100

15

100

ADRs EGFR

(2 3)

40mg

LUX-Lung3(1200.32) 57% LUX-Lung6(1200.34) 33.1% LUX-Lung8 (1200.125) 25% / 1.3% 0% (LUX-Lung3) 0% 2.5% LUX-Lung6 3.8% 2.0% LUX-Lung8

4257 LUX- Ä

LUX-Lung 3 1200.32 229 EGFR TKI
40mg 1 111
40mg 1 /
ADR 100% 96% /
95% 15% 89% 6% 57%
ADR
96% 52%
1 40mg /
ADR 8% 12% ADR
1.3% 0%

LUX-Lung 6 1200.34 239 EGFR TKI
40mg 1 113 /
40mg 1 /
ADR 98.7% 99.1% /
90.0% 15.0% / 81.2% 9.7%
33.1% ADR

1 40mg /
ADR 10.0% 39.8% ADR
0% 2.5%

LUX-Lung8 1200.125 392 NSCLC 40mg
1 , 395 150mg 1
28 39 10% 50mg
ADR 93% 81%
70% 33%
67% 67% 27%
11% 5%

40mg 50mg NSCLC

EGFR EGFR NSCLC 40 mg

1200.22, 1200.32, 1200.34, 1200.123 497 EGFR TKI NSCLC 50 mg 1200.23, 1200.33 1200.41, 1200.42 1638 EGFR TKI NSCLC

40mg 50mg 1

ADR EGFR

40mg 50mg 1 ADR LUX-Lung 3

40mg 50mg 58.8% 53.1% CTCAE1 2 ADR 2

2 ADR CTCAE 1 2

40mg 50mg 38%

41% CTCAE 3 4 ADR CTCAE3 ADR

ADR 7% 11.7%

EGFR NSCLC

ADR 2

2 EGFR NSCLC

	N=497	N=1638
	14.3%	11.8%
	9.9%	17.6%
	1.2%	1.9%
	0.6%	4.5%

40mg 1 0.2% 4 50mg

1 0.1% 4 3 0.2% 4

LUX-Lung8 40mg

ADR EGFR

LUX-Lung 3 ADR 65% CTCAE 1

2 CTCAE 3/4 9.9%/0.5% CTCAE 3 5.9%

11% ADR

3.8% 2.0%

3 40mg 50mg NSCLC ADRs

ADR ≥1/10 ≥1/100

<1/10 ≥1/1,000 <1/100 ≥1/10,000 <1/1,000

<1/10,000

3 ADRs

	≥1/10	**≥1/100 <1/10**	**≥1/1,000 1/100**
	1		
	2		
		ALT AST	
	3 4 5 6	8	Stevens-Johnson 7 7
		/	

1
2
3
4
5
6
7
8

-
- /Stevens-Johnson

2 3 6

6

12 48 2 3

4257 1.6%

ILD

P-gp P-gp

2

P- P-gp

P-gp P-gp

P-gp

P-gp A

P-gp

C_{max} 50% $AUC_{0-\infty}$

39%

I 160mg 1

3 100mg 1 2

2 360mg

EGFR(ErbB1) HER2(ErbB2) HER4(ErbB4)

ErbB

EGFR EGFR 19

21 L858R T790M

HER2

EGFR HER2 EGFR L858R/7790M

26

52

Ames 1

Muta™ 4

4 6 8mg/kg

6mg/kg 40mg AUC

8mg/kg

40mg AUC 0.63

4

2

- 5mg/kg

40mg AUC 0.2

10mg/kg 40mg AUC 0.7

-

16mg/kg 40mg AUC 2

1h 6h

80 150

3T3

2-5 C_{max}

20mg 50mg C_{max} $AUC_{0-\infty}$

50% C_{max} 39% $AUC_{0-\infty}$

3

1 $AUC_{\tau,ss}$ 26%

3 1

92% $AUC_{0-\infty}$

95%

15mg 85.4% 4.3%

88% 37

8 2.77 AUC 2.11 C_{max}

5%

“

”

50mg Child

Phildh A 1 Tf2.5 0 Td[<098521513<01CF>Tj1.989 0 Td[Tf13.0.9B14D6>8634D7C /.9 <>-10.8 <123B84C940 1 Tf0

“

”

Child Pugh C

927 764 NSCLC

28-87

1 62kg 1 42kg 2.5

$AUC_{\tau,ss}$ 26% 1 95kg 97.5

22%

$AUC_{\tau,ss}$ 15%

927 6 9

CrCL CrCL 79mL/min

CrCL CrCL 60 30mL/min

$AUC_{\tau,ss}$ 13% 42% CrCL 90 120mL/min

6% 20%

ECOG

P- (P-gp)

P-

2 P-gp

1 200mg 2 3 40mg

6

119% ($AUC_{0-\infty}$) 104% (C_{max})

6 111% ($AUC_{0-\infty}$) 105%

(C_{max}) 2 200mg 2 3 20mg

1 48% ($AUC_{0-\infty}$) 39% (C_{max})

P-gp 600mg 7 40mg

34% ($AUC_{0-\infty}$) 22% (C_{max})

P-gp

P-gp

P-gp

BCRP

BCRP

OATB1B1 OATP1B3 OATP2B1 OAT1 OAT3 OCT1 OCT2

OCT3 -

P450 CYP

CYP

CYP -

2%

FMO3 CYP3A4 N-

CYP

CYP

CYP

UDP- 1A1 UGT1A1

UGT1A1 -

30

10 / / / 10 / 3 / /

36

8

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