

!" #&/  
4;O <548G=>3> 70AB>AC20==O ;V:0@AL:>3> 70A>1C

\$□#□®  
(FLUNOL®)

!::04:

4VNG0 @5G>28=0: fluconazole;

1 :0?AC;0 =07>;C 150 <3;

4>?>28=8: ;0:B>78 <=>3V4@0B, :@>E<0;L :C:C@C47O=89, :@5<=VN 4V>:A84 :>;>W4=89 1572>4=89,  
<03=VN AB50@0B, =0B@VN ;0C@8;AC;LD0B;

:0?AC;0 65;0B8=>20 B25@40: 65;0B8=, B8B0=C 4V>:A84 (171), 07>@C1V= (122).

V:0@AL:0 D>@<0. □0?AC;8.

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 1 7 :@8H5G:>N @>652>3> :>;L>@C B0

:>@?CA>< 1V;>3> :>;L>@C, I>4=>@V4=89 ?>@>H>: 1V;>3> :>;L>@C.

\$0@<0:>B5@0?52B8G=0 3@C?0.

@>B83@81:>2V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O, ?>EV4=V B@807>;C. >4 "% J02A C01.

\$0@<0:>;>3VG=V 2;0AB82>ABV.

\$0@<0:>48=0

\$.C:>=07>; O2;OT A>1>N 0:B82=C @5G>28=C 3@C?8 B@807>;C. @5?0@0B 70AB>A>2CNBL 4;O

;V:C20==O ?>25@E=528E V A8AB5<=8E 3@81:>28E V=D5:FV9. 0 @0EC=>: ?>BC6=>3> V=3V1C20==O

D5@<5=BC 14α-45<5B8;078 3@81:>2>W ;;VB8=8 2V= ?@83=VGCT A8=B57 5@3>AB5@>;C, >A=>2=>3>

:>=5=B0 <5<1@0= ;;VB8= 3@81V2 V ?;VA=O28. '8=8BL DC=3VAB0B8G=C 4VN V T 0:B82=8 2V4=>A=>

G8A5;L=8E ?0B>35==8E 3@81V2, B0:8E O: *Candida spp. (C.albicans, C. tropicalis), Cryptococcus*

*neoformans, Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, Sporothrix schenkii,*

*Paracoccidioides brasiliensis, C. glabrata, B0 1V;LH>ABV 45@<0B>DVVB2. \$.C:>=07>; <5=H 0:B82=89*

*2V4=>A=> spergillus spp. B0 enicillium marneffeii, =5 4VT =0 3@818 C. krusei, Fussarium spp. B0 783>*

*\$0@<0:>:V=5B8:0.*

\$.C:>=07>; 4>1@5 01A>@1CTBLAO ?VA;O ?5@>@0;L=>3> ?@89>3> 1V>4>ABC?=VABL ?5@528ICT 90

% .8H5 11-12 % D;C:>=07>;C 72O7CNBLAO 7 1V;;0<8 ?;07<8 :@>2V. 1T< @>7?>4V;C ?@81;87=> B0:89

A0<89, O: V >1T< @>7?>4V;C 2>48 2 >@30=V7=07>; 4>1@5 ?@>=8:0T 2 CAV @V48=8 >@30=V7@. 0:A8

<0;L=V @V2=V 22V 4>AO30NBLAO ?@>BO3>< 0,5-1,5 3>48=8, 1V>;>3VG=89 ?5@V>4 =0?V2@>7?04C

AB0=>28BL <0965 30 3>48= (I> T ?V4AB02>N 4;O >4=>@07>2>3> 70AB>AC20==O ?@5?0@0BC C

;V:C20==V 203V=0;L=>3> :0=484>7C; 70 2AV<0 V=H8<8 ?>:070==O<8 D;C:>=07>; 70AB>A>2C20B8 1

@07 =0 4>1C). 5=H5 5 % D;C:>=07>;C <5B01>;V7CTBLAO ?V4 G0A ?5@H>3> ?@>E>465==O G5@57

?5GV=:C. @81;87=> 80 % D;C:>=07>;C =5 707=0T <5B01>;V748BLAO =8@:0<8, 70;8H>: 282>48BLAO C

283;04V <5B01>;VBV2.

;V=VG=V E0@0:B5@8AB8:8.

>:070==O.

>AB@89 203V=0;L=89 :0=484>7, :>;8 @5G=>N.

0=484>7=89 10;0=VB, :>;8 @5G=>N.

@>B8?>:070==O.

V?5@GCB;82VABL 4> D;C:>=07>;C, 4> V=H8E 07>;L=8E A?>;C:01> 4> 1C4L-O:>W 7 4>?>28=

?@5?0@0BC.

4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 B5@D5=048=C ?0FVT=B0<, O:V 70AB>A>2CNBL

D;C:>=07>; 1030B>@07>2> C 4>70E 400 <3/4>1C B0 28I5 (73V4=> 7 @57C;LB0B0<8 4>A;V465==O 270T

<>4VW 1030B>@07>2>3> 70AB>AC20==O).

4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 V=H8E ;V:0@AL:8E 70A>1V2, I> ?>4>26CNBL V=B5@20;  
QT B0 <5B01>;V7CNBLAO 70 4>?><3>N D5@<5=BC CYP4 (=0?@8:;04 F870?@84C, 0AB5;C, ?V  
<>784C, EV=V48=C B0 5@8B@>

**70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.**

@>B8?>:070=5 ACAC20==O D;C:>=07>;C B0 =86G5707=0G5=8E ;V:0@AL:8E 70A>1V2.

&870?@84. >2V4><;O;>AO ?@> @>728B>: ?>1VG=8E @50:FV9 7 1>:C A5@FO, C B> ?0@>:A87<0;L=C  
H;C=>G:>2C B0EV:0@4VN B8?C «?V@C5B» C ?0FVT=BV2, O:V >4=>G0A=> 70AB>A>2C20;8  
D;C:>=07>; B0 F870?@84. >=B@>;L>20=5 4>A;V465==O ?@>45<=>AB@C20;>; I> >4=>G0A=5  
70AB>AC20==O 200 <3 D;C:>=07>;C 1 @07 =0 4>1C B0 20 <3 F870?@84C 4 @078 =0 4>1C ?@872>48;>  
4> 7=0G=>3> ?V428I5==O @V2=O F870?@84C C ?;072V B0 4> ?>4>265==O V=B5@20;C QT. 4=>G0A=5  
70AB>AC20==O D;C:>=07>;C B0 F870?@84C ?@>B8?>:070=5.

"5@D5=048=. '5@57 28?04:8 @>728B:C B06:8E A5@F528E 0@8B4>265==O< V=B5@20;C QTc, C  
?0FVT=BV2, O:V 70AB>A>2CNBL 07>;L=V ?@>B83@81:>2V ;V:0@AL:V 70A>18 >4=>G0A=> 7  
B5@D5=048=><, 1C;8 ?@>2545=V 4>A;V465==O 270T<>4VW F8E ?@5?0@0BV2. # E>4V >4=>3>  
4>A;V465==O ?@8 70AB>AC20==V D;C:>=07>;C C 4>7V 200 <3 =0 4>1C =5 1C;> 28O2;5=> ?>4>265==O  
V=B5@20;C QTc. =H5 4>A;V465==O ?@8 70AB>AC20==V D;C:>=07>;C C 4>70E 400 <3 B0 800 <3 =0  
4>1C ?@>45<=>AB@C20;>; I> 70AB>AC20==O D;C:>=07>;C C 4>70E 400 <3 =0 4>1C 01> 28I5 7=0G=>  
?V428ICT @V25=L B5@D5=048=C C ?;072V ?@8 >4=>G0A=>AC20==V F8E ?@5?0@0BV2. !CAC20==O  
D;C:>=07>;C C 4>70E 400 <3 01> 28I5 7 B5@D5=048=>< ?@>B8?>:070=5. @8 70AB>AC20==V  
D;C:>=07>;C C 4>70E =86G5 400 <3 =0 4>1C >4=>G0A=> 7 B5@D5=048=>< A;V4 ?@>2>48B8  
@5B5;L=89 <=>VB>@8=3 AB0=C ?0FVT=B0.

AB5;. !CAC20==O D;C:>=07>;C B0 0AB5;C <>65 7<5=H8B8 ;V@5=A 0AB5;C. !?@8G8=5=5 F8<  
?V428I5==O :>=F5=B@0FVW 0AB5;C C ?;072V <>65 ?@8725AB8 4> ?>4>265==O V=B5@20;C QT B0 C  
@V4:VA=8E 28?04:0E 4> ?0@>:A87<0;L=>W H;C=>G:>2>W B0EV:0@4VW B8?C «?V@C5B». 4=>G0A=5  
70AB>AC20==O D;C:>=07>;C B0 0AB5;C ?@>B8?>:070=5.

V<>784 B0 EV=V48=. !CAC20==O D;C:>=07>;C B0 ?V<>784C 01> EV=V48=C <>65 ?@872>48B8 4>  
?@83=VG5==O <5B01>;V7in vitro B0 in vivo =5 ?@>2>48;8. V428I5==O :>=F5=B@0FVW ?V<>784C 01>  
EV=V48=C C ?;072V <>65 A?@8G8=OB8 ?>4>265==O V=B5@20;C QT B0 C @V4:VA=8E 28?04:0E  
?@872>48B8 4> @>728B:C ?0@>:A87<0;L=>W H;C=>G:>2>W B0EV:0@4VW B8?C «?V@C5B». 4=>G0A=5  
70AB>AC20==O D;C:>=07>;C B0 ?V<>784C 01> EV=V48=C ?@>B8?>:070=5.

@8B@> 4=>G0A=5 70AB>AC20==O 5@8B@>=07>;C ?>B5=FV9=> <>65 ?@872>48B8 4> ?V428I5==O  
@878:C @>728B:C :0@4V>B>:A8G=>ABV (?>4>265==O V=B5@20;C QT, ?0@>:A87<0;L=0 H;C=>G:>20  
B0EV:0@4VO B8?C «?V@C5B») B0, O: =0A;V4>;, 4> @0?B>2>W A5@F52>W A<5@BV. 0AB>AC20==O  
:><1V=0FVW 40=8E ;V:0@AL:8E 70A>1V2 ?@>B8?>:070=5.

5 @5:><5=4CTBLAO >4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 =86G5707=0G5=8E ;V:0@AL:8E  
70A>1V2.

0;>D0=B@8=. \$;C:>=07>; <>65 A?@8G8=8B8 ?V428I5==O :>=F5=B@0FVW 30;>D0=B@8=C C ?;072V 70  
@0EC=>: ?@83=VG5==O CYP3A4. 4=>G0A=5 70AB>AC20==O F8E ;V:0@AL:8E 70A>1V2 ?>B5=FV9=>  
<>65 ?@872>48B8 4> ?V428I5==O @878:C @>728B:C :0@4V>B>:A8G=>ABV (?>4>265==O V=B5@20;C  
QT, ?0@>:A87<0;L=0 H;C=>G:>20 B0EV:0@4VO B8?C «?V@C5B») B0, O: =0A;V4>;, 4> @0?B>2>W  
A5@F52>W A<5@BV. !;V4 C=8:0B8 70AB>AC20==O :><1V=0FVW 40=8E ;V:0@AL:8E 70A>1V2.

!CAC20==O D;C:>=07>;C B0 =86G5707=0G5=8E ;V:0@AL:8E 70A>1V2 28<030T >15@56=>ABV B0  
:>@83C20==O 4>78.

?;82 V=H8E ;V:0@AL:8E 70A>1V2 =0 D;C:>=07>;.

>A;V465==O 270T<>4VW ?@>45<=>AB@C20;8, I> >4=>G0A=5 26820==O W6V, F8<5B848=, 0=B0F848  
01> ?>40;LH5 ?>@>3> BV;0 4;O ?5@5A04:8 :VAB:>2>3><>7:C =5 <0T ;V=VG=> 7=0GCI>3> 2?;82C =0  
01A>@1FVN D;C:>=07>;C ?@8 9>3> ?5@>@0;L=>AC20==V.

8D0 4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 @8D048;> 4> 7=865==O ?;>IV ?V4 :@82>N  
«:>=F5=B@0FVO-G0A» (AUC) =0 25 % B0 A:>@>GC20;> ?5@V>4 =0?V2282545==O D;C:>=07>;C =0  
20 %. ">A>2CNBL @8D073;O=CB8 4>FV;L=VABL ?V428I5==O 4>78 D;C:>=07>;C.

?;82 D;C:>=07>;C =0 V=HV ;V:0@AL:V 70A>18.

\$;C:>=07>; T ?>BC6=8< V=3V1VB>@>< V7>D5@<5=BC 2C9 F8B>E@>AC20==V V7 D;C:>=07>;>  
VA=CT @878: ?V428I5==O C ?;072V :>=F5=B@0FV9 V=H8E A?>;C, I> <5B01>;V7CNBLAO CYP2C9,  
CYP2C19 B0 CYP3A4. ">A>2C20B8 B0:V :><1V=0FVW ?@5?0@0BV2 A;V4 7 >15@56=VABN; ?@8 FL>

1EV4=> @5B5;L=> A?>AB5@V30B8 70 AB0=< ?0FVT=BV2. @83=VGC20;L=0 4VO D;C:>=07>;C =0  
D5@<5=B8 715@V30TBLAO ?@>BO3<< 4- 5 4V1 ?VA;O 9>3> 70AB>AC20==O C 7207:C 7 9>3>  
B@820;8< ?5@V>4<< =0?V2282545==O.  
;LD5=B0=V;. V4 G0A >4=>G0A=>3> 70AB>AC20==O 0;LD5=B0=V;C C 4>7V 20=07>;C C 4>7V 400 <3  
74>@>28< 4>1@>2>;LFO< A?>AB5@V30;>AO 42>@07>25 71V;LH5==O AUC<sub>10</sub>, <>6;82>, G5@57  
V=3V1C20==O CYP3A4. >65 1CB8 =5>1EV4=8< :>@83C20==O 4>78 0;LD5=B0=V;C.  
, =>@B@8?B8;V=. \$;C:>=07>; ?>A8;NT 4VN 0@B@8?B8;V=C. 5:><5=4CTBLAO 28=F5=B@0FVW 5-  
=>@B@8?B8;V=C B0/01> S-0G0B:C :><1V=>20=>W B5@0?VW B0 G5@57 1 B8645=L. # @07V  
=5>1EV4=>ABV A;V4 2V4:>@83C20B8 4>7C 0@B@8?B8;V=C.  
B5@8F8=. 4=>G0A=5 70AB>AC20==O D;C:>=07>;C B0 0B5@8F8=C V=DV:>20=8< <8H0< V7 =>@  
<0;L=8< V< B0 V=DV:>20=8< <8H0< 7V 7=865=8< V< ?@8725;> 4> B0:8E @57C;LB0BV2: =525;8:89  
048B82=89 ?@>B83@81:>289 5D5:B ?@8 A8AB5<=V9 V=D5:FVW C. *albicans*, 2V4ACB=VABL 270T  
<>4VW ?@8 2=CB@VH=L>G5@5?>V9 V=D5:FVW *Cryptococcus neoformans* B0 0=B03>=V7< 42>E  
?@5?0@0BV2 ?@8 A8AB5<=V9 V=D5:FVW *Aspergillus fumigatus*. ;V=VG=5 7=0G5==O @57C;LB0BV2,  
>B@8<0=8E C E>4V F8E 4>A;V465=L, =52V4<<5.  
=B8:>03C;O=B8. /: V ?@8 70AB>AC20==V V=H8E 07>;L=8E ?@>B83@81:>28E 70A>1V2, ?@8  
>4=>G0A=>AC20==V D;C:>=07>;C B0 20@D0@8=C ?>2V4<<;O;>AO ?@> 28?04:8 @>728B:C :@>2>B5G  
(35<0B<<, =>A>2>W :@>2>B5GV, H;C=:>2>-.8H:>28E :@>2>B5G, 35<0BC@VW B0 <5;5=8) C  
?>T4=0==V 7 ?>4>265==O< ?@>B@><1V=>2>3> G0AC. @8 >4=>G0A=>AC20==V D;C:>=07>;C B0  
20@D0@8=C A?>AB5@V30;>AO 42>:@0B=5 ?V428I5==O ?@>B@><1V=>2>3> G0AC, V<>2V@=>,  
2=0A;V4>: ?@83=VG5==O <5B01>;V7 :>=B@>;N20B8 ?@>B@><1V=>289 G0A C ?0FVT=BV2, O:V  
>4=>G0A=> 70AB>A>2CNBL :C<0@8=>2V 0=B8:>03C;O=B8. >65 1CB8 =5>1EV4=>N :>@5:FVO 4>78  
20@D0@8=C.  
5=7>4V075?V=8 :>@>B:>W 4VW, =0?@8:;04;0<, B@807>;0 @87=0G5==O D;C:>=07>;C ?VA;O  
?5@>@0;L=>3> 70AB>AC20==O ;048;> 4> 7=0G=>3> ?V428I5==O :>=F5=B@0FVW ;0 ?>A8;5==O ?A8E>  
<>B>@=8E 5D5:BV2. 4=>G0A=5 70AB>AC20==O D;C:>=07>;C C 4>7V 200 <3 B0 ;07V 7,5 <3  
?5@>@0;L=> ?@872>48;> 4> ?V428I5==O AUC B0 ?5@V>4C =0?V2282545==O C 3,7 B0 2,2 @070  
2V4?>2V4=>. 0AB>AC20==O D;C:>=07>;C C 4>7V 200 <3/4>1C B0 0,25 <3 B@807>;0@0;L=>  
?@872>48;> 4> ?V428I5==O AUC B0 ?5@V>4C =0?V2282545==O C 4,4 B0 2,3 @070 2V4?>2V4=>. @8  
>4=>G0A=>AC20==V D;C:>=07>;C B0 B@807>;0AB5@V30;>AO ?>B5=FVN20==O B0 ?@>;>=30FVO  
5D5:BV2 B@807>;0  
/:I> ?0FVT=BC, O:89 ?@>E>48BL :C@A ;V:C20==O D;C:>=07>;<, A;V4 >4=>G0A=> ?@87=0G8B8  
B5@0?VN 15=7>4V075?V=0<8, 4>7C >AB0==VE A;V4 7<5=H8B8 B0 2AB0=>28B8 =0;56=89 =03;04 70  
AB0=<< ?0FVT=B0.  
0@10<075?V=. \$;C:>=07>; ?@83=VGCT <5B01>;V7< :0@10<075?V=C B0 A?@8G8=OT ?V428I5==O  
@V2=O :0@10<075?V=C 2 A8@>20BFV :@>2V =0 30%. A=CT @878: @>728B:C ?@>02V2  
B>:A8G=>ABV 7 1>:C :0@10<075?V=C. >65 1CB8 =5>1EV4=8< :>@83C20==O 4>78 :0@10<075?V=C  
70;56=> 2V4 @V2=O 9>3> :>=F5=B@0FVW B0 4VW ?@5?0@0BC.  
;>:0B>@8 :0;LFVT28E :0=0;V2. 5O:V 0=B03>=VAB8 :0;LFVN (=VD548?V=, VA@048?V=, 0<;>48?V= B0  
D5;>48?V=) <5B01>;V7CNBLAO D5@<5=B>< CYP3A4. \$;C:>=07>; ?>B5=FV9=> <>65 ?V428IC20B8  
A8AB5<=C 5:A?>78FVN 1;>:0B>@V2 :0;LFVT28E :0=0;V2. 5:><5=4>20=89 @5B5;L=89 <=>VB>@8=3  
I>4> @>728B:C ?>1VG=8E @50:FV9.  
?5:>:A8I. @8 >4=>G0A=>AC20==V D;C:>=07>;C (200 <3 =0 4>1C) B0 F5;5>:A81C (200 <3) <0:A8<0;L=0  
:>=F5=B@0FVO (C<sub>max</sub>) B0 AUC F5;5>:A81C ?V428IC20;8AO =0 68% B0 134% 2V4?>2V4=>. @8  
>4=>G0A=>AC20==V F5;5>:A81C B0 D;C:>=07>;C <>65 1CB8 =5>1EV4=8< 7<5=H5==O 4>78  
F5;5>:A81C 242VGV.  
?>D>AD0 4=>G0A=5 70AB>AC20==O F8;>D>AD0=07>;C ?@872>48BL 4> ?V428I5==O @V2=O  
1V;V@C1V=C B0 :@50B8=V=C 2 A8@>20BFV :@>2V. &V ?@5?0@0B8<>6=0 70AB>A>2C20B8  
>4=>G0A=>, 72060NG8 =0 @878: ?V428I5==O :>=F5=B@0FVW 1V;V@C1V=C B0 :@50B8=V=C 2  
A8@>20BFV :@>2V.  
\$5=B0=V;. >2V4<<;O;>AO ?@> >48= ;5B0;L=89 28?04>: V=B>:A8:0FVW D5=B0=V;< 2=0A;V4>:  
<>6;82>W 270T<>4VW D5=B0=V;C B0 D;C:>=07>;C. > B>3> 6, C 4>A;V465==V 7 CG0ABN 1274>@>28E  
4>1@>2>;LFV2 1C;> ?@>45<=>AB@>20=>, I> D;C:>=07>; 7=0G=> C?>2V;L=N202 5;V=F5=B@0FVW  
D5=B0=V;C <>65 ?@8725AB8 4> ?@83=VG5==O 48E0==O, B> :>=B@>;N20B8 AB0= ?0FVT=B0. >65  
1CB8 =5>1EV4=>N :>@5:FVO 4>78 D5=B0=V;C.

=3V1VB>@8 ->@54C:B078. !CAC20==O D;C:>=07>;C B0 V=3V1VB>@V2 -oA-@54C:B078, I>  
<5B01>;V7CNBLAO CYP3A4 (0B>@20AB0B8= B0 A8<20AB0B8=), 01> V=3V1VB>@V2 -oA-  
@54C:B078, I> <5B01>;V7CNBLAO CYP2C9 (D;C20AB0B8=), ?V428ICT @878: @>728B:C ?0BVW B0  
@014>;V7C. # @07V =5>1EV4=>ABV >4=>G0A=>3> 70AB>AC20==O F8E ?@5?0@0BV2 A;V4  
@5B5;L=> A?>AB5@V30B8 70 ?0FVT=B<< I>4> 28=8:=5==O A8?0BVW B0 @014>;V7C V ?@>2>48B8  
<=>VB>@8=3 @V2=O :@50B8=:V=078. # 28?04:C 7=0G=>3> ?V428I5==O @V2=O :@50B8=:V078, 0  
B0:>6 ?@8 4V03=>ABC20==V 01> ?V4>7@V =0 ?0BVN/@014>;V7 70AB>AC20==O V=3V1VB>@V2 -  
oA-@54C:B078 A;V4 ?@8?8=8B8.

AC?@5A>@8 (=0?@8:;04 F8:;>A?>@8=, 525@>;V;V;V  
?>A?>@8=. \$;C:>=07>; 7=0G=> ?V428ICT :>=F5=B@0FVN B0 AUC F8:;>A?>@8=C. @8 >4=>G0A=>  
AC20==V D;C:>=07>;C C 4>7V 200 <3/4>1C B0 F8:;>A?>@8=C C 4>7V 2,7 <3/3/4>1C A?>AB5@V30;>AO  
71V;LH5==O AUC F8:;>A?>@8=C C 1,8 @070. &V ?@5?0@0B8 <6=0 70AB>A>2C20B8 >4=>G0A=> 70 C  
<>28 7<5=H5==O 4>78 F8:;>A?>@8=C 70;56=> 2V4 9>3> :>=F5=B@0FVW.

25@>;V %>G0 4>A;V465=L in vitro B0 in vivo =5 ?@>2>48;8, D;C:>=07>; <65 ?V428IC20B8  
:>=F5=B@0FVN 525@>;V20BFV :@>2V G5@57 ?@83=VG5==O CYP34.

!8@>;V \$;C:>=07>; ?V428ICT :>=F5=B@0FVN A8@>;V2V, V<>2V@=>, H;OE<< ?@83=VG5==O  
<5B01>;V7;V 2V4 @V2=O :>=F5=B@0FVW B0 5D5:BV2 ?@5?0@0BC.

"0:@>;V \$;C:>=07>; <65 ?V428IC20B8 :>=F5=B@0FVW B0:@>;V20BFV :@>2V 4> 5 @07V2 ?@8 9>3>  
?5@>@0;L=>AC20==V G5@57 ?@83=VG5==O <5B01>;V7;VAC20==V B0:@>;VAB5@V30;>AO  
7=0G=8E 7FVNNBLAO V7 =5D@>B>:A8G=VABN. >7C B0:@>;V@0;L=>3> 70AB>AC20==O A;V4  
7=86C20B8 70;56=> 2V4 :>=F5=B@0FVW B0:@>;V

>70@B0=. \$;C:>=07>; ?@83=VGCT <5B01>;V7< ;>70@B0=C 4> 9>3> 0:B82=>3> <5B01>;VBC (E- 3174),  
I> 7C<>2;NT 1V;LHC G0AB8=C 0=B03>=V7 @5F5?B>@V2 0=3V>B5=78=C II ?V4 G0A 70AB>AC20==O  
;>70@B0=C. 5:><5=4>20=> 74V9A=N20B8 ?>ABV9=89 <=>VB>@8=3 0@B5@V0;L=>3> B8A:C C  
?0FVT=BV2.

5B04>=. \$;C:>=07>; <65 ?V428IC20B8 :>=F5=B@0FVN <5B04>=C C A8@>20BFV :@>2V. @8  
>4=>G0A=>AC20==V <5B04>=C B0 D;C:>=07>;C <65 1CB8 =5>1EV4=8< :>@83C20==O 4>78  
<5B04>=C.

5AB5@>W4=V ?@>B870?0;L=V 70A>18 (). @8 >4=>G0A=>AC20==V 7 D;C:>=07>;< C<sub>max</sub> B0 AUC  
D;C@1V?@>D5=C ?V428IC20;8AO =0 23 % B0 81 % 2V4?>2V4=> ?>@V2=O=> 7 2V4?>2V4=8<8  
?>:07=8:0<8 ?@8 70AB>AC20==V BV;L:8 D;C@1V?@>D5=C. =0;>3VG=> ?@8 >4=>G0A=>AC20==V  
D;C:>=07>;C 7 @0F5<sub>max</sub> B0 AUC D0@<0>;>3VG=> 0:B82=>3> V7<<5@C S-(+)-V1C?@>D5=C  
?V428IC20;8AO =0 15 % B0 82 % 2V4?>2V4=> ?>@V2=O=> 7 B0:8<8 ?>:07=8:0<8 ?@8 70AB>AC20==V  
BV;L:8 @0F53> V1C?@>D5=C.

%>G0 A?5FV0;L=8E 4>A;V465=L =5 ?@>2>48;8, D;C:>=07>; ?>B5=V9=> 740B=89 ?V428IC20B8 A8AB5  
<=C 5:A?>78FVN V=H8E , I> <5B01>;V7CNBLAO CYP2C9 (=0?@8:;04 =0?@>:A5=C, ;>@=>:A8:0  
D5=0:C). 5:><5=4>20=> ?5@V>48G=> 74V9A=N20B8 <=>VB>@8=3 ?>1VG=8E @50:FV9 B0 B>:A8G=8E  
?@>O2V2, ?>2O70=8E V7 . >65 7=04>18B8AO :>@83C20==O 4>78 .

\$5=VB>W=. \$;C:>=07>; ?@83=VGCT <5B01>;V7< D5=VB>W=C 2 ?5GV=FV. 4=>G0A=5 1030B>@07>25  
70AB>AC20==O 200 <3 D;C:>=07>;C B0 250 <3 D5=VB>W=C 2=CB@VH=L>25==> ?@872>48BL 4>  
?V428I5==O AUC<sub>24</sub> D5=VB>W=C =0 75 % B0 !<sub>min</sub>=0 128 %. @8 >4=>G0A=>AC20==V F8E ;V:0@AL:8E  
70A>1V2 A;V4 ?@>2>48B8 <=>VB>@8=3 :>=F5=B@0FVW D5=VB>W=C C A8@>20BFV :@>2V 4;O  
C=8:=5==O @>728B:C B>:A8G=>W 4VW D5=VB>W=C.

@54=V7>=. >2V4><;O;>AO ?@> 28?04>;. :>;8 C ?0FVT=B0 ?VA;O B@0=A?;0=B0FVW ?5GV=:8 =0 B;V  
70AB>AC20==O ?@54=V7>=C @>728=C;0AO 3>AB@0 =54>AB0B=VABL :>@8=04=8@:>28E 70;>7, I>  
28=8:;0 ?VA;O ?@8?8=5==O B@83> :C@AC B5@0?VW D;C:>=07>;>AC20==O D;C:>=07>;C, V<>2V@=>,  
A?@8G8=8;> ?>A8;5==O 0:B82=>ABV CYP3A4, I> ?@8725;> 4> ?@8H284H5==O <5B01>;V7=C. !;V4  
@5B5;L=> AB568B8 70 ?0FVT=B0<8, O:V ?@>B03<< B@820;>3> G0AC >4=>G0A=> 70AB>A>2CNBL  
D;C:>=07>; B0 ?@54=V7>=, 7 <5B>N ?>?5@5465==O @>728B:C =54>AB0B=>ABV :>@8 =04=8@:>28E  
70;>7 ?VA;O ?@8?8=5==O 70AB>AC20==O D;C:>=07>;C.

8D01CB8=. \$;C:>=07>; ?V428ICT :>=F5=B@0FVN @8D01CB8=C 2 A8@>20BFV :@>2V, I> ?@872>48BL  
4> 71V;LH5==O AU! @8D01CB8=C 4> 80%. @8 >4=>G0A=>AC20==V D;C:>=07>;C B0 @8D01CB8=C  
?>2V4><;O;>AO ?@> 28?04:8 @>728B:C C25WBC. @8 70AB>AC20==V B0:>W :><1V=0FVW  
;V:0@AL:8E 70A>1V2 A;V4 1@0B8 4> C2038 A8=8 B>:A8G=>W 4VW @8D01CB8=C.

!0:2V=02V@. \$;C:>=07>; ?V428ICT AUC B0 C<sub>max</sub> A0:2V=02V@C ?@81;87=> =0 50 % B0 55 %  
2V4?>2V4=> G5@57 ?@83=VG5==O <5B01>;V7=07>;< B0 A0:2V=02V@>