

!" #&/
4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC

\$#□"®
(FUNIT)

!::04:

4VNG0 @5G>28=0: Vtraconazol5;

1 :0?AC;0 =07>;C 100 <3;

4>?>28=8: 3V4@>:A8?@>?V;<5B8;F5;N;>70, ?>;V5B8;5=3;V:>;L 6000;

=59B@0;L=V ?5;5B8: FC:>@ AD5@8G=89, :@>E<0;L :C:C@C47O=89;

65;0B8=>20 :0?AC;0: 07>@C1V= (122), ?0B5=B>20=89 A8=V9 V (131), B8B0=C 4V>:A84 (171), :0@0 <5;L (150), 65;0B8=.

V:0@AL:0 D>@<0. □0?AC;8.

\$0@<0:>B5@0?52B8G=0 3@C??. @>B83@81:>2V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O. >EV4=V B@807>;C. >4 " ! J02A C02.

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

>:070==O.

V:>78, A?@8G8=5=V GCB;828<8 4> VB@0:>=07>;C 71C4=8:0<8: 2C;L2>203V=0;L=89 :0=484>7; 45@ <0B>;>3VG=V/>DB0;L<>;>3VG=V 3@81:>2V 70E2>@N20==O - 45@<0B>7, 28AV2:>?>4V1=89 ;8H09, 3@81:>289 :5@0B8B; >@0;L=89 :0=484>7; >=VE>78, A?@8G8=5=V 45@<0B>DVB0<8 B0/01> 4@V6460 <8; A8AB5<=V 78 - A8AB5<=89 0A?5@3V;L>7 01> :0=484>7, :@8?B>:>:>7, 2;;NG0NG8 :@8?B>:>:>289 <5=V=3VB (V>A;01;5=8< ?0FVT=B0< V7 :@8?B>:>:>7< B0 2AV< ?0FVT=B0< 7 :@8?B>:>:>7< F5=B@0;L=>W =5@2>2>W A8AB5<8 V=B@0:>=07>; ?@87=0G0TBLAO ;8H5 C @07V =55D5:B82=>ABV ;V:C20==O V=H8<8 ?@>B83@81:>28<8 ?@5?0@0B0<8); 3VAB>?;07<>7, A?>@>B@8E>7, ?0@0:>:F84V>W4>7, 1;0AB>7 B0 V=HV A8AB5<=V 78, I> 7CAB@VG0NBLAO 2:@09 @V4:>.

@>B8?>:070==O.

0?AC;8 \$C=VB® ?@>B8?>:070=V ?0FVT=B0< V7 2V4><>N 3V?5@GCB;82VABN 4> ?@5?0@0BC 01> 9>3> :>=5=BV2.

@>B8?>:070=5 >4=>G0A=5 70AB>AC20==O =0ABC?=8E ;V:0@AL:8E 70A>1V2 V7 :0?AC;0<8 \$C=VB® (482. @>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»);

- AC1AB@0BV2 CYP3A4, O:V <>6CBL ?>4>26C20B8 V=B5@20; QT, B0:8E O: 0AB5;, 15?@848;; F870?@84, 4>D5B8;V4, ;520F5B8;<5B04>; (;52<>5B048;); ;0AB8=, ?V<>784, EV=V48=, A5@B8=4>; B0 B5@D5=048=. 4=>G0A=5 70AB>AC20==O <>65 A?@8G8=8B8 ?V428I5==O :>=F5=B@0FV9 F8E

;V:0@AL:8E 70A>1V2 C ?;072V, I><>65 ?@8725AB8 4> ?>4>265==O V=B5@20;C QT B0 7@V4:0 4> 28?04:V2 B@V?>BV==O-<5@5EBV==O H;C=>G:V2:

- V=3V1VB>@V2 HMG-CoA @54C:B078, O:V <5B01>;V7CNBLAO CYP3A4, B0:8E O: 0B>@20AB0B8=, ;>20AB0B8= B0 A8<20AB0B8=;

- B@807>;0@0;L=>3> ;0

- 0;0;>W4V2 @V6:V2, =0?@8::04 483V4@>5@3>B0<5B@8= (5@3>=>2V=), 5@3>B0

- 5;5B@8?B0=C;

- =V7>;48?V=C.

@>B8?>:070=> 70AB>AC20==O :0?AC; \$C=VBC® ?0FVT=B0< 7V H;C=>G:>2>N 48ADC=:FVTN, B0:>N O: 70ABV9=0 A5@F520 =54>AB0B=VABL, 01> 70ABV9=>N A5@F52>N =54>AB0B=VABN 2 0=0=57V, 70 28=OB:><; ;V:C20==O V=D5:FV9, I> 703@>6CNBL 68BBN (482. @>74V; «A>1;82>ABV

70AB>AC20==O»).

5 A;V4 70AB>A>2C20B8 :0?AC;8 \$C=VB® ?V4 G0A 203VB=>ABV, 70 28=OB:><; ;V:C20==O AB0=V2, I> 703@>6CNBL 68BBN <0B5@V (482. @>74V; «0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O

3@C44N»).

!>AV1 70AB>AC20==O B0 4>78.

0AB>A>2CNBL 2=CB@VH=L>. ;O >?B8<0;L=>W 01A>@1FVW ?@5?0@0BC =5>1EV4=>
 70AB>A>2C20B8 :0?AC;8 \$C=VB® 2V4@07C ?VA;O W48. 0?AC;8 A;V4 :>2B0B8 FV;8<8.
 !E5<8 ;V:C20==O 4>@>A;8E 4;O :>6=>3> ?>:070==O =0ABC?=V:

>:070==O 4;O 70AB>AC20==O	>70	"@820;VABL
V=5;>;>3VG=V 70E2>@N20==O		
" C;L2>203V=0;L=89 :0=484>7	200 <3 2 @078 =0 4>1C 01> 200 <3 1 @07 =0 4>1C	1 45=L 01> 3 4=V
5@<0B>;>3VG=V/>DB0;L<>;>3VG=V 70E2>@N20==O		
" 8AV2:>?>4V1=89 ;8H09	200 <3 1 @07 =0 4>1C	7 4=V2
" 5@<0B>78	200 <3 1 @07 =0 4>1C	7 4=V2
@8 C@065==V 4V;O=>: 7V 7=0G=8< ABC?5=5< :5@0B8=V70FVW (=0?@8;;04, 5?V45@ <>DVBVO :8AB59 @C: B0 AB>?) =5>1EV4=5 ;V:C20==O 4>70<8 200 <3 2 @078 =0 4>1C ?@>BO3>< 7 4=V2.		
" @0;L=V :0=484>78	100 <3 1 @07 =0 4>1C	15 4=V2
!;V4 71V;LH8B8 4>7C 4> 200 <3 1 @07 =0 4>1C ?@>BO3>< 15 4=V2 C ?0FVT=BV2 V7 =59B@>?5=VTN 01> !>< G5@57 ?>@CH5==O 01A>@1FVW ?@5?0@0BC 2 F8E ?0FVT=BV2.		
" @81:>289 :5@0B8B	200 <3 1 @07 =0 4>1C	21 45=L
" =VE>78 (157?5@5@2=5 ;V:C20==O)	48= :C@A A.;040TBLAO 7 ?@89<0==O 42>E :0?AC; \$C=VBC 2 @078 =0 4>1C (?> 200 <3 2 @078 =0 4>1C) ?@>BO3>< 1 B86=O.	;O ;V:C20==O 3@81:>28E C@065=L =V3BL>28E ?;0AB8=>: =0 @C:0E @5:> <5=4CTBLAO 2 :C@A8. ;O ;V:C20==O 3@81:>28E C@065=L =V3BL>28E ?;0AB8=>: =0 ?0;LFOE =V3 @5:> <5=4CTBLAO B@8 :C@A8. 5@5@20 ;V=VG=V @57C;LB0B8 1C4CBL ?@>O2;OB8AO ?VA;O 7025@H5==O ;V:C20==O 2 2V4@>AB0==O =V3BV2.

V:C20==O >=VE>7V2, A?@8G8=5=8E 45@<0B>DVB0<8 B0/01> 4@V6460<8, <>65 B0:>6 ?@>2>48B8AO
 V7 70AB>AC20==O< ?C;LA-B5@0?VW (482. B01;8FN =86G5).

>:0;V70FVO >=VE> 7V2	"86=V				
	1-9	2-9, 3-9, 4-9	5-9	6-9, 7-9, 8-9	9-9
#@065==O =V3BL>28E ?;0AB8=>: =0 ?0;LFOE =V3, O: 7 C@065==O< =V3BV2 =0 @C:0E, B0: V 157 =L>3>	1-9 :C@A ?C;LA- B5@0?VW	"86=V, ?@>BO3>< O:8E =5 ?@89 <0NBL VB@0:>=07>;	2-9 :C@A ?C;LA- B5@0?VW	"86=V, ?@>BO3>< O:8E =5 ?@89 <0NBL VB@0:>=07>;	3-9 :C@A ?C;LA- B5@0?VW

#@065==O =V3BL>28E ?;0AB8=>: BV;L:8 =0 @C:0E	1-9 :C@A ?C;LA- B5@0?VW	"86=V, ?@>BO3<< O:8E =5 ?@89 <0NBL VB@0:>=07>;	2-9 :C@A ?C;LA- B5@0?VW	
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?B8<0;L=V ;;V=VG=V B0 ;>3VG=V 5D5:B8 4>AO30NBLAO G5@57 2-4 B86=V ?VA;O 70:V=G5==O
;V:C20==O V=D5:FV9 H:V@8, 2C;L2>203V=0;L=8E :0=484>7V2 B0 >@0;L=8E :0=484>7V2, B0 G5@57 6-
9 28E ?;0AB8=>:. &5 ?>2O70=> 7 B8<, I> 282545==O VB@0:>=07>;C 7 B:0=8= H:V@8, =V3BV2 V
A;87>28E >1>;>=>: 2V41C20TBLAO ?>2V;L=VH5, =V6 V7 ?;07<8 :@>2V.

"@820;VABL ;V:C20==O A8AB5<=8E 3@81:>28E C@065=L ?>28==0 :>@83C20B8AO 70;56=> 2V4
>3VG=>W B0 ;;V=VG=>W 2V4?>2V4V =0 B5@0?VN:

!8AB5<=V 78			
>:070==O 4;O 70AB>AC20==O	>7C20==O	!5@54=O B@820;VABL ;V:C20==O	@8
A?5@3V;L>7	200 <3 1 @07 =0 4>1C	2-5	1V;LH5==O 4>78 4> 200 <3 2 @078 =0 4>1C C 28?04:C V=20782=>3> 01> 48A520=>3> 70E2>@N20==O
0=484>7	100-200 <3 1 @07 =0 4>1C	2V4 3 B86=V2 4> 7	1V;LH5==O 4>78 4> 200 <3 2 @078 =0 4>1C C 28?04:C V=20782=>3> 01> 48A520=>3> 70E2>@N20==O
@8?B>:>:>7 (157 >7=0: <5=V=3VBC)	200 <3 1 @07 =0 4>1C	2V4 2 1 @>:C	
@8?B>:>:>289 <5=V=3VB	400 <3 1 @07 =0 4>1C	2V4 2 1 @>:C	V4B@874V; «A>1;82>ABV 70AB>AC20==O»).
VAB>?;07<>7	2V4 200 <3 1 @07 =0 4>1C 4> 200 <3 2 @078 =0 4>1C	8	
!>@>B@8E>7	100 <3 1 @07 =0 4>1C	3	
0@0:>:F84V>W4>- 7	100 <3 1 @07 =0 4>1C	6	0=8E I>4> 5D5:B82=>ABV 707=0G5=>3> @5687C20==O C E2>@8E =0 !=54>AB0B=L>
%@><>7	100 - 200 <3 1 @07 =0 4>1C	6	
;0AB>7	2V4 100 <3 1 @07 =0 4>1C 4> 200 <3 2 @078 =0 4>1C	6	

>1VG=V @50:FVW.

>1VG=V @50:FVW ?@5?0@0BC A8AB5<0B87>20=V 2V4=>A=> :>6=>W V7 A8AB5< >@30=V2 70;56=>
2V4 G0AB>B8 7 28:>@8AB0==O< =0ABC?=>W ;:0A8DV:0FVW: 4C65 G0AB> (≥1/10), G0AB> (≥1/100 V
<1/10), =5G0AB> (≥1/1000 V <1/100), @V4:> (≥1/10000 V <1/1000), 4C65 @V4:> (<1/10000), 2;:NG0NG8
>:@52V4><;5==O.

=D5:FVW B0 V=207VW:

4C65 @V4:> V=D5:FVW 25@E=VE 48E0;L=8E H;OEV2.

I>:C ;VW A8AB5<8 B0 :@>2V:

4C65 @V4:> ;59:>?5=VO, =59B@>?5=VO, B@><1>F8B>?5=VO.

I>:C VW A8AB5<8:

4C65 @V4:> A8@>20B:>20 E2>@>10; 0=3V>=52@>B8G=89 =01@O.; 0=0DV;0:B8G=V, 0=0DV;0:B>W4=V B0 0;5@3VG=V @50:FVW.

I>:C <5B01>;V7

4C65 @V4:> 3V?>:0;VT:0;LFVT

I>:C =5@2>2>W A8AB5<8:

4C65 @V4:> ?5@8D5@8G=0 =59@>?0BVO, ?0@5AB57VO, 3V?>5AB57VO, 3>;>2=89 1V;L, 70?0 <>@>G5==O.

I>:C >@30=0 7>@C:

4C65 @V4:> ?>@CH5==O 7>@C, 2;;NG0NG8 ?>@C B0 48?;>?VN.

I>:C >@30=0 A;CEC B0 25AB81C;O@=>3> 0?0@0BC:

4C65 @V4:> B8=VB, B820 G8 ABV9:0 2B@0B0 A;CEC.

I>:C A5@FO:

4C65 @V4:> 70ABV9=0 A5@F520 =54>AB0B=VABL.

I>:C >@30=V2 48E0==O:

4C65 @V4:> =01@O; ;535=L, 48A?=>5, @8=VB, A8=CA8B.

I>:C H;C=:>2>-.:8H:>2>3> B@0:BC:

4C65 @V4:> ?0=:@50B8B, 1V;L C 682>BV, =C4>B0, 1;N20==O, 48A?5?AVO, 4V0@5O, 70?>@, 4873527VO, 74CBBO 682>B0.

I>:C 35?0B>1V;V0@=>W A8AB5<8:

4C65 @V4:> A5@9>7=0 35?0B>B>:A8G=VABL (2;;NG0NG8 ?>>48=>:V 28?04:8 ;5B0;L=>W 3>AB@>W ?5GV=:>2>W =54>AB0B=>ABV), 35?0B8B, >1>@>B=5 71V;LH5==O @V2=O ?5GV=:>28E D5@<5=BV2.

I>:C H;V@8 B0 ?V4H;V@=>W ;;VB:>28=8:

4C65 @V4:> B>:A8G=89 5?V45@<0;L=89 =5:@>;V7, A8=4@<< !BV25=A0-6>=A>=0, 3>AB@89 35=5@0;V7>20=89 5:70=B5<0B>7=89 ?CABC;L>7, @<=0 5@8B5< 0, 5:AD>;V0B82=89 45@<0B8B, ;59:>F8B>;;0AB8G=89 20A:C;VB, A2VB;>GCB;82VABL, 28A8?0==O, :@>?820=:0, 0;>?5FVO, A25@1V6.

I>:C <07>2>-A:5;5B=>W A8AB5<8:

4C65 @V4:>

I>:C A5G>284V;L=>W A8AB5<8:

4C65 @V4:> ?>;0:VC@VO, =5B@8<0==O A5GV.

I>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7:

4C65 @V4:> @>7;048 <5=AB@C0;L=>3> F8.;C, 5@5:B8;L=0 48ADC=:FVO.

030;L=V @>7;048:

5G0AB> =01@O:8, ?V@5:AVO.

5@54>7C20==O.

>2V4><;5=L ?@> 28?04:8 ?5@54>7C20==O =5<0T.

/:I> B@0?8;>AL 28?04:>25 ?5@54>7C20==O, A;V4 268B8 ?V4B@84V2. @>BO3>< ?5@H>W 3>48=8 ?VA;O ?@89>A;V4 ?@<8B8 H;C=>.: /:I> F5 28?@0240=>, <>6=0 ?@87=0G8B8 0:B82>20=5 2C3V;;O. B@0:>=07>; =5 <>6=0 2825AB8 H;OE>< 35<>4V0;V7C. !?5F8DVG=>3> 0=B84>BC =5<0T.

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

03VB=VABL

\$C=VB® =5 A;V4 ?@87=0G0B8 203VB=8<, >:@V< 28?04:V2 A8AB5<=8E ;59:>7V2, O:V 703@>6CNBL 68BBN, :>;8 ?>B5=FBV9=0 :>@8ABL 4;O <0B5@V ?5@528ICT @878: =530B82=>3> 2?;82C =0 ?;V4 (482. @>74V; «@>B8?>:070==O»).

V=:8 4VB>@>4=>3> 2V:C

V=:0< 4VB>@>4=>3> 2V:C, O:V ?@89<0NBL :0?AC;8 \$C=VB®, A;V4 70AB>A>2C20B8 =04V9=V 70A>18 :>=B@0F5?FVW ?@>BO3>< CAL>3> :C@AC ;V:C20==O 4> =0AB0==O ?5@H>W <5=AB@C0FVW ?VA;O 9>3> 7025@H5==O.

5@V>4 3>4C20==O 3@C44N

C65 =57=0G=V :V;L:>ABV VB@0:>=07>;C 284V;ONBLAO C 3@C4=5<>;>:>. ">4 3>4C20==O 3@C44N
=5>1EV4=> 7VAB028B8 <>6;8289 @878: 4;O 48B8=8 7 >GV:C20=>N :>@8ABN 2V4 ;V:C20==O
?@5?0@0B<< \$C=VB® 4;O <0B5@V. # AC<=V2=8E 28?04:0E 6V=FV A;V4 ?@8?8=8B8 3>4C20==O
3@C44N.

VB8.

5 @5:><5=4CTBLAO 70AB>A>2C20B8 4OBO

A>1;82>ABV 70AB>AC20==O.

5@5E@5A=0 3V?5@GCB;82VABL

5<0T 40=8E I>4> ?5@5E@5A=>W GCB;82>ABV =07>;< B0 V=H8<8 07>;>28<8 ?@>B83@81:>28<8
70A>10<8. !;V4 1CB8 >15@56=8<8 ?@8 ?@87=0G5==V :0?AC; VB@0:>=07>;C ?0FVT=B0< 7
3V?5@GCB;82VABN 4> V=H8E 07>;V2.

?;82 =0 A5@F5

@5?0@0B =5 A;V4 ?@89<0B8 ?0FVT=B0< V7 70ABV9=>N A5@F52>N =54>AB0B=VABN 01> 7
=0O2=VABN FL>3> 70E2>@N20==O 2 0=0<=57V 70 28=OB:<< 28?04:V2, :>;8 >GV:C20=0 :>@8ABL
7=0G=> ?5@528ICT ?>B5=FV9=89 @878:.. @8 V=482V4C0;L=V9 >FV=FV A?V22V4=>H5==O :>@8ABL
/@878: A;V4 72060B8 =0 B0:V D0:B>@8, O: 206:VABL ?>:070==O, @568< 4>7C20==O B0 B@820;VABL
;V:C20==O (7030;L=0 4>1>20 4>70) B0 V=482V4C0;L=V D0:B>@8 @878:C 28=8:=5==O 70ABV9=>W
A5@F52>W =54>AB0B=>ABV. &V D0:B>@8 @878:C 2:;NG0NBL =0O2=VABL A5@F528E
70E2>@N20=L, B0:8E O: VH5@>10 A5@FO 01> C@065==O ;:0?0=V2; BO6:V 70E2>@N20==O ;535=V2,
B0:V O: >1AB@C:B82=V C@065==O ;535=V2; =8@:>20 =54>AB0B=VABL 01> V=HV 70E2>@N20==O,
I> AC?@>2>46CNBLAO =01@O:0<8. "0:8E ?0FVT=V2 A;V4 ?@>V=D>@>7=0:8 B0 A8<8 70ABV9=>W
A5@F52>W =54>AB0B=>ABV, ;V:C20==O A;V4 ?@>2>48B8 7 >15@56=VABN, ?V4 G0A ;V:C20==O
=5>1EV4=> :>=B@>;N20B8 A8<8 70ABV9=>W A5@F52>W =54>AB0B=>ABV. @8 ?>O2V F8E A8
AC20==O ?@5?0@0BC =5>1EV4=> ?@8?8=8B8.

;:>:0B>@8 :0;LFVT28E :0=0;V2 <>6CBL <0B8 =530B82=89 V=>B@>?=89 5D5:B, O:89 <>65 ?>A8;N20B8
F59 65 5D5:B VB@0:>=07>;C. "0:>6 VB@0:>=07>; <>65 ?@83=VGC20B8 <5B01>;V7< 1;:>:0B>@V2
:0;LFVT28E :0=0;V2. ">B@815@56=>ABV ?@8 >4=>G0A=>AC20==V VB@0:>=07>;C B0 1;:>:0B>@V2
:0;LFVT28E :0=0;V2 G5@57 71V;LH5==O @878:C 28=8:=5==O 70ABV9=>W A5@F52>W
=54>AB0B=>ABV (482. @>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T
<>4V9»).

?;82 =0 ?5GV=:C

060=> ?@>2>48B8 <>=VB>@8=3 DC=:FVW ?5GV=:8 C ?0FVT=V2, O:V ?@89<0NBL VB@0:>=07>;.
0FVT=V2 =5>1EV4=> ?>?5@548B8 ?@> =5>1EV4=VABL B5@2>3> 725@=5==O 4>;V:0@O C 28?04:C
?@>O2C >7=0: 01> A81EV4=> =5309=> ?@8?8=8B8 ;V:C20==O V ?@>25AB8 4>A;V465==O
?5GV=:>2>W DC=:FVW. 0FVT=B0< V7 ?V428I5=8< @V2=5< ?5GV=:>28E D5@<5=V2, 0:B82=8<
70E2>@N20==O< ?5GV=:8 01> 7 ?@>O20<8 35?0B>B>:A8G=>ABV 2V4 V=H8E ?@5?0@0BV2
;V:C20==O @>7?>G8=0NBL BV;L:8 70 C<>28, I> >GV:C20=89 @57C;LB0B ?5@528ICT @878:
?>H:>465==O ?5GV=:8. # B0:8E 28?04:0E =5>1EV4=89 <>=VB>@8=3 ?5GV=:>28E D5@<5=V2.

=865==O :8A;>B=>ABV H;C=:0

@8 7=865=V9 :8A;>B=>ABV H;C=:0 01A>@1FVO VB@0:>=07>;C ?>3V@HCTBLAO. 0FVT=B8, O:V
>4=>G0A=> 70AB>A>2CNBL ?@5?0@0B8 4;O 7=865==O :8A;>B=>ABV (B0:V O: 0;N:A84), <0NBL
4>B@8=09<5=H5 2-3>48==>W ?5@5@28 <0<8 F8E ;V:0@AL:8E 70A>1V2. 0FVT=B0< 7
0E;>@3V4@VTN, =0?@8:;04 E2>@8< =0 !G8 B8<, O:V ?@89<0NBL 2-1;:>:0B>@8 01> V=3V1VB>@8
?@>B==>W ?><5=4CTBLAO ?@89<0B8 :0?AC;8 VB@0:>=07>;C 7 =0?>O<8 B8?C :>;0.
0FVT=B8 ;VB=L>3> 2V:C

@5?0@0B =5 A;V4 70AB>A>2C20B8 ?0FVT=B0< ;VB=L>3> 2V:C, O:I> BV;L:8 :>@8ABL 2V4
70AB>AC20==O ?5@52060T ?>B5=FV9=89 @878:.

>@CH5==O DC=:FVW ?5GV=:8

!;V4 1CB8 >15@56=8<8 ?@8 70AB>AC20==V ?@5?0@0BC FV9 :0B53>@VW ?0FVT=V2.

>@CH5==O DC=:FVW =8@>:

!;V4 1CB8 >15@56=8<8 ?@8 70AB>AC20==V ?@5?0@0BC FV9 :0B53>@VW ?0FVT=BV2.
V>4>ABC?=VABL VB@0:>=07>;C ?@8 ?5@>@0;L=>AC20==V C ?0FVT=BV2 7 =8@:>2>N
=54>AB0B=VABN <>65 1CB8 7=865=0. # FL>
B@0B0 A;CEC
C;8 ?>2V4><;5==O ?@> B82C G8 ABV9:C 2B@0BC A;CEC C ?0FVT=BV2, O:V ?@89<0NBL
VB@0:>=07>;. # 45O:8E 28?04:0E 2B@0B0 A;CEC 2V41C20;0AL =0 B;V >4=>G0A=>3> 70AB>AC20==O
7 EV=V48=<<, O:89 ?@>B8?>:070=89 (482. @>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0
V=HV 2848 270T<>4V9»). !;CE 70728G09 2V4=>2;NTBLAO ?VA;O 70:V=G5==O B5@0?VW ?@5?0@0B<
>4=0: C 45O:8E ?0FVT=BV2 2B@0B0 A;CEC T =572>@>B=>N.
0FVT=B8 7 VN =54>AB0B=VABN

45O:8E ?0FVT=BV2 7 VN =54>AB0B=VABN (=0?@8:;04, ?0FVT=B8 7 =59B@>?5=VTN, !< G8
B@0=A?;0=B>20=8<8 >@30=0<8) ?5@>@0;L=0 1V>4>ABC?=VABL VB@0:>=07>;C <>65 1CB8 7=865=0.
0FVT=B8 7 V7 A8AB5<=8<8 3@81:>28<8 V=D5:FVO<8, I> 157?>A5@54=L> 703@>6CNBL 68BBN
'5@57 D0@<0:>:V=5B8G=V 2;0AB82>ABV (482. @>74V; «\$0@<0:>:V=5B8:0») ?@5?0@0B =5 @5:>
<5=4CTBLAO 70AB>A>2C20B8 4;O ?5@28==>W B5@0?VW =52V4:;04=8E AB0=V2, A?@8G8=5=8E
A8AB5<=8<8 3@81:>28<8 V=D5:FVO<8.
0FVT=B8, E2>@V =0 !

?0FVT=BV2, E2>@8E =0 !, O:V ;V:C20;8 A8AB5<=C 3@81:>2C V=D5:FVN, B0:C O: A?>@>B@8E>7,
1;0AB>7, 3VAB>?;07<>7 G8 :@8?B>:>:7 (<5=V=350;L=89 G8 =5<5=V=350;L=89), B0 C O:8E VA=CT
703@>70 @5F8482C ;V:0@ ?>28=5=>FV=8B8 =5>1EV4=VABL ?V4B@8> ;V:C20==O.
59@>?0BVO

@8 28=8:=5==V =59@>?0BVW, ?>2O70=>W V7 70AB>AC20==O< ?@5?0@0BC, A;V4 ?@8?8=8B8
;V:C20==O.

>7;048 2C3;52>4=>3> >I

0FVT=B8 7 @V4:VA=8<8 A?04:>28<8 E2>@>10<8 =5?5@5=>A8<>ABV D@C:B>78, <0;L01A>@1FVTN
3;N:>78-30;0:B>78 G8 A0E0@07>-V7<0;LB07=>N =54>AB0B=VABN =5 ?>28==V 70AB>A>2C20B8 F59
;V:0@AL:89 70AV1.

5@5E@5A=0 @578AB5=B=VABL

/:I> ?@8 70E2>@N20==V =0 A8AB5<=89 :0=484>7 T ?V4>7@0 =0 B5, I> 2848 3@81V2 Candida, O:V
28:;8:0NBL 70E2>@N20==O, @578AB5=B=V 4> D;C:>=07>;C, =5 <>6=0 AB25@46C20B8, I> 2>=8
1C4CBL GCB;828<8 4> VB@0:>=07>;C. ">1EV4=> 28:>=0B8 B5AB =0 GCB;82VABL ?5@54 ?>G0B:<
;V:C20==O ?@5?0@0B>

>B5=FV0; 270T<>4VW

@5?0@0B <>65 270T<>4VOB8 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 (482. @>74V; «70T<>4VO 7 V=H8<8
;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). B@0:>=07>; A;V4 70AB>A>2C20B8 =5 @0=VH5,
=V6 G5@57 420 B86=V ?VA;O 7025@H5==O ;V:C20==O V=4C:B>@0<8 CYP3A4 (@8D0<, @8D01CB8=>
<, D5=>10@1VB0;<<, D5=VB>W=<<, :0@10<075?V=<<, 5:AB@0:B>< 72V@>1>N (Hipericum perforatum)
) . 0AB>AC20==O VB@0:>=07>;C >4=>G0A=> 7 F8<8 ;V:0<8 <>65 ?@8725AB8 4> =54>AB0B=L>W
B5@0?52B8G=>W :=F5=B@0FVW VB@0:>=07>;C 2 ?;072V4=>, 4> =55D5:B82=>ABV ;V:C20==O.

**40B=VABL 2?;820B8 =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> @>1>BV 7
V=H8<8 <5E0=V7<0<8.**

!;V4 ?0<OB0B8 ?@> <>6;82VABL 28=8:=5==O B0:8E ?>1VG=8E @50:FV9, O: 70?0<>@>G5==O, @>7;048
7>@C B0 2B@0B0 A;CEC, I> <>65 ?@8725AB8 4> =530B82=8E =0A;V4:V2 ?V4 G0A :5@C20==O
02B>B@0=A?>@B< B0 @>1>B8 7 V=H8<8 <5E0=V7<0<8.

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

1. V:0@AL:V 70A>18, I> 2?;820NBL =0 01A>@1FVN VB@0:>=07>;C.

V:0@AL:V 70A>18, O:V 7=86CNBL :8A;>B=VABL H;C=:0, 7=86CNBL 01A>@1FVN VB@0:>=07>;C.

2. V:0@AL:V 70A>18, I> 2?;820NBL =0 <5B01>;V7< VB@0:>=07>;C.

B@0:>=07>; <5B01>;V7CTBLAO ?5@5206=> G5@57 A8AB5E@>CYP3A4.

4=>G0A=5 70AB>AC20==O VB@0:>=07>;C 7 @8D0<, @8D01CB8=>< B0 D5=VB>W=<< =5 @5:>

<5=4CTBLAO. >BC6=V V=3V1VB>@8 D5@<5=BC !Y 4, B0:V O: @8B>=02V@, V=48=02V@, :;0@8B@>

3. ?;82 VB@0:>=07>;C =0 <5B01>;V7< V=H8E ;V:0@AL:8E 70A>1V2.

B@0:>=07>; <>65 ?@83=VGC20B8 <5B01>;V7< ;V:0@AL:8E 70A>1V2, I> @>7I5?;NNBLAO D5@<5=B0

<8 B8?C F8B>E@>Y 4. 57C;LB0B>< FL>3> <>65 1CB8 ?>A8;5==O 01> ?>4>265==O WE 4VW,
2;:NG0NG8 ?>1VG=V @50:FVW. @8 >4=>G0A=>AC20==V A;V4 725@=CB8AO 70 V=D>@<0FVTN I>4>
<548G=>3> 70AB>AC20==O 2V4?>2V4=>3> ;V:0@AL:>3> 70A>1C. VA;O ?@8?8=5==O ;V:C20==O
@V2=V VB@0:>=07>;C 2 ?;072V 7=86CNBLAO ?>ABC?>2>, 70;56=> 2V4 4>7 B0 B@820;>ABV
;V:C20==O. &5 A;V4 1@0B8 4> C2038 ?@8 >FV=FV ?@83=VGC20;L=>3> 5D5:BC VB@0:>=07>;C =0
<5B01>;V7< ?@5?0@0BV2, I> 70AB>A>2CNBLAO >4=>G0A=>.
0ABC?=V ;V:0@AL:V 70A>18 ?@>B8?>:070=V 4> 70AB>AC20==O ?V4 G0A ;V:C20==O VB@0:>=07>;>
- AB5;, 15?@848;, F870?@84, 4>D5B8;V4, ;520F5B8;<5B04>; (;52<5B048;), ;0AB8=, ?V<>784, EV=V48=,
A5@B8=4>;, B5@D5=048=, >A:V;L:8 F5 <>65 ?@8725AB8 4> 7=0G=>3> 71V;LH5==O :>=F5=B@0FVW
F8E AC1AB@0BV2 C ?;07 <>65 A?@8G8=8B8 ?>4>265==O V=B5@20;C QT B0 @V4:VA=8E 28?04:V2
B@V?>BV==O-<5@5EBV==O.
- =3V1VB>@8 HMG-CoA @54C:B078, I> <5B01>;V7CNBLAO CYP3A4, B0:V O: 0B>@20AB0B8=,
;>20AB0B8= B0 A8<20AB0B8=.
- "@807>;0< B0 ;0< 4;O ?5@>@0;L=>3> 70AB>AC20==O.
- :;0;>W48 @V6:V2, B0:V O: 483V4@>5@3>B0<5B@8= (5@3=>=2V=), 5@3>B0
- ;5B@8?B0=.
- 87>;48?V=.
@8 >4=>G0A=>AC20==V VB@0:>=07>;C B0 1;>:0B>@V2 :0;LFVT28E :0=0;V2 =5>1EV4=> 4>B@8
15@56=>ABV, >A:V;L:8 F5 <>65 ?@8725AB8 4> 71V;LH5==O @878:C 70ABV9=>W A5@F52>W
=54>AB0B=>ABV. >40B:>2> 4> <>6;828E D0@<0:>.V=5B8G=8E 270T<>4V9 V7 70;CG5==O< D5@<5=BC
CYP3A4, 1;>:0B>@8 :0;LFVT28E :0=0;V2 <>6CBL A?@8G8=0B8 =530B82=89 V=>B@?>=89 5D5:B, O:89
<>65 ?>A8;N20B8 ?>4V1=89 5D5:B VB@0:>=07>;C.
V:0@AL:V 70A>18, ?@8 ?@87=0G5==V O:8E =5>1EV4=89 :>=B@>;L 70 @V2=5< WE :>=F5=B@0FVW
2 ?;071VG=8<8 5D5:B0<8 (?@8 >4=>G0A=>=07>;< 4>7C 707=0G5=8E ?@5?0@0BV2, 70
=5>1EV4=>ABV, A;V4 7<5=HC20B8):
" ?5@>@0;L=V 0=B8:>03C;O=B8;
" V=3V1VB>@8 -?@>B5078, B0:V O: @8B>=02V@, V=48=02V@, A0:2V=02V@;
" 45O:V ?@>B8?CE;8==V ?@5?0@0B8, B0:V O: 0;:0;>W48 10@2V=:C @>652>3> (Vinca), 1CAC;D0=,
4>F5B0:A5; B0 B@8<5B@5:A0B;
" 1;>:0B>@8 :0;LFVT28E :0=0;V2, I> @>7I5?;NNBLAO D5@<5=B>< CYP3A4, B0:V O:
483V4@>?V@848= B0 25@0?0
" 45O:V VAC?@5A82=V 70A>18: F8;:>A?>@8=, B0:@>;V6 2V4><89 O: A8@>;V
" 45O:V ?@5?0@0B8, I> @>7I5?;NNBLAO D5@<5=B>< CYP3A4 - V=3V1VB>@8 @54C:B078 HMG
-Co, B0:V O: 0B>@20AB0B8=;
" 45O:V 3;N:>:>@B8:>W48, B0:V O: 1C45A>=V4, 45:A0<5B07>=, D;CB8:07>=, <5B8;?@54=V7>;>;
" 483>:A8= (G5@57 V=3V1C20==O -3;V:>?@>B5W=C);
" V=HV ?@5?0@0B8: :0@10<075?V=, F8;>AB07>;, 1CA?V@>=, 487>?V@0;0<, 1@>B87>;0<, ;0< 2/2,
@8D01CB8=, 510AB8=, D5=B0=V;;, 30;>D0=B@8=, @5?03;V=V4 B0 @51>:A5B8=. 06;82VABL
71V;LH5==O WE :>=F5=B@0FV9 B0 ;V=VG=0 7=0GCIVABL F8E 7=>G0A=>AC20==V 7 VB@0:>=07>;>
< 70A>2CTBLAO.

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

\$0@<0:>48=0

B@0:>=07>; - ?>EV4=5 B@807>;C, <0T H8@>:89 A?5:B@ 4VW.

B@0:>=07>; ?@83=VGCT A8=B57 5@3>AB5@>;C C ;:VB8=0E 3@81:V2. @3>AB5@>; T 206;828< :>
=5=B>< ;:VB8=>W <5<1@0=8 3@81:0, ?@83=VG5==O 9>3> A8=B57C 70157?5GCT ?@>B83@81:>289
5D5:B.

!B>A>2=> VB@0:>=07>;C, 3@0=8G=V 7=0G5==O 2AB0=>2;5=V ;8H5 4;O *Candida spp.* ;O ?>25@E=528E
B8G=8E V=D5:FV9 (CLSI M27-A2, 3@0=8G=V 7=0G5==O =5 2AB0=>2;5=V 70 <5B>4>;>3VTN EUCAST
) . @0=8G=V 7=0G5==O CLSI =0ABC?=V: GCB;82V ≤0,125; GCB;82V 4>7>- 70;56=V 0,25 0,5 B0
@578AB5=B=V ≤1

B@0:>=07>; ?@83=VGCT @VAB H8@>:>3> A?5:B@0 3@81:V2, ?0B>35==8E 4;O ;N48=8 C
:>=F5=B@0FV9 70728G09 ≤1 (*Trichophyton spp.*, *Microsporum spp.*, *Epidermophyton floccosum*), 4@V646V
(*Candida spp.*, 2;:NG0NG8 *C. albicans*, *C. glabrata* B0 *C. krusei*, *Cryptococcus neoformans*, *Pityrosporum spp.*,
Trichosporon spp., *Geotrichum spp.*), *Aspergillus spp.*, *Histoplasma spp.*, *Paracoccidioides brasiliensis*, *Sporothrix*

schenkii, Fonsecaea spp., Cladosporium spp., Blastomyces dermatitidis, Coccidioides immitis, Pseudallescheria boydii, Penicillium marneffei B0 V=HV @V7=>2848 4@V646V2 B0 3@81:V2.
Candida krusei, Candida glabrata B0 *Candida tropicalis* 7030;>< T =09<5=H GCB;828<8 2840<8 *Candida*, 0 45O:V V7>;OB8 45<>=AB@CNBL @578AB5=B=VABL 4> VB@0:>=07>;C.
>;>2=8<8 B8?0<8 3@81:V2, O:V =5 ?@83=VGCNBLAO VB@0:>=07>;><, T 783>*Rhizopus spp., Rhizomucor spp., Mucor spp., B0 Absidia spp., Fusarium spp., Scedosporium proliferans* B0 *Scopulariopsis spp.*
\$0@<0:>:V=5B8:0.

IA>@1FVO

B@0:>=07>; H284:> 2A<>:BCTBLAO ?VA;O ?5@>@0;L=>3> 70AB>AC20==O. 0:A8<0;L=V ?;07<>2V :>=F5=B@0FVW ?VA;O ?@89>4>AO30NBLAO 2?@>4>26 2-5 3>48=. 1A>;NB=0 1V>;>3VG=0 4>ABC?=VABL VB@0:>=07>;C AB0=>28BL 55 %. 0:A8<0;L=0 1V>4>ABC?=VABL ?@8 70AB>AC20==V 2=CB@VH=L> A?>AB5@V30TBLAO ?@8 26820==V 2V4@07C ?VA;O ?@89>:>0;>@V9=>W W6V. >7?>4V;

V;LH0 G0AB8=0 VB@0:>=07>;C 7207CTBLAO 7 1V;:0<8 ?;07<8 (99,8 %), C G>;>2=8< 7207CNG8< :> =5=B>< (99,6 % 4;O 3V4@>:A8<5B01>;VBC). "0:>6 2V= <0T 28A>;C 0DV==VABL 4> 68@V2. 8H5 0,2 % VB@0:>=07>;C 2 :@>2V 70;8H0TBLAO C 283;O4V =572070=>W @5G>28=8. #O2=89 >1T< @>7?>4V;C VB@0:>=07>;C 4>A8BL 7=0G=89 (>700 ;), 7 G>3> <>6=0 ?@8?CAB8B8 9>3> >1H8@=89 @>7?>4V; C B:0=8=0E: :>=F5=B@0FVW C ;535=OE, =8@:0E, ?5GV=FV, :VAB:0E, H;C=:C, A5;57V=FV B0<O70E 1C;8 C 2-3 @078 28IV 70 :>=F5=B@0FVW C ?;070:>?8G5==O VB@0:>=07>;C 2 :5@0B8=>28E B:0=8=0E, >A>1;82> 2 H:V@V, 2 4 @078 ?5@528IC20;> B0:5 C ?;072V.

V>B@0=AD>@<0FVO

B@0:>=07>; 7=0G=>N N @>7I5?;NTBLAO 2 ?5GV=FV 7 CB2>@5==O< 25;8:>W :V;L:>ABV <5B01>;VBV2. 4=8< V7 B0:8E <5B01>;VBV2 T 3V4@>:AVVB@0:>=07>;, O:89<0T ?>@V2=O=C 7 VB@0:>=07>;>< ?@>B83@81:>2C 4VN *in vitro*. >=F5=B@0FVW 3V4@>:AVVB@0:>=07>;C 2 ?;07C 2 @078 28IV, =V6 :>=F5=B@0FVW VB@0:>=07>;C. 3V4=> 7 4>A;V465==O<8 *in vitro*, CYP3A4 3>;>2=89 D5@<5=B, 70;CG5=89 4> ?@>F5AC <5B01>;V7 =07>;C.

82545==O

@81;87=> 35 % VB@0:>=07>;C 5:A:@5BCTBLAO C 283;O4V =50:B82=8E <5B01>;VBV2 V7 A5G5N B0 1;87L:> 54 % 7 :0;>82545==O 28EV4=>W ;V:0@AL:>W @5G>28=8 =8@:0<8 AB0=>28BL <5=H =V6 0,03 % 4>78, 2 B>9 G0A O: 282545==O =57W @5G>28=8 7 :0;>< 20@VNTBLAO 2V4 3 4> 18 %. ;V@5=A VB@0:>=07>;C 7=86CTBLAO 70 28I8E 4>7 G5@57 =0A8GC20=89 ?5GV=>289 <5B01>;V7 V=V9=VABL/=5;V=V9=VABL =0A;V4>: =5;V=V9=>W D0@<0:>:V=5B8:8 VB@0:>=07>; 0:C4>26 1030B>@07>2>3> 4>7C20==O. V2=>206=V :>=F5=B@0FVW 4>AO30NBLAO ?@>BO3>< 15 4=V2, 7=0G5==O C_{max} B0 AUC C 4-7 @07V2 28IV, =V6 ?VA;O >4=>@07>2>3> 70AB>AC20==O. !5@54=V9 ?5@V>4 =0?V2282545==O AB0=>28BL 40 3>48= ?VA;O ?>2B>@N20=8E 4>7.

A>1;82V :0B53>@VW ?0FVT=BV2

5GV=:>20 =54>AB0B=VABL: D0@<0:>:V=5B8G=5 4>A;V465==O V7 70AB>AC20==O< >4=>@07>2>W 4>78 100 <3 VB@0:>=07>;C (1 :0?AC;8 100 <3) 1C;> ?@>2545=> A5@54 6 74>@>28E B0 12 E2>@8E =0 F8@>7 ?0FVT=BV2. 5 A?>AB5@V30;>AO ;V=VG=> 7=0GCI>W @V7=8FV AUC_∞ C_{max} (47 %) B0 71V;LH5==O C 2 @078 ?5@V>4C =0?V2282545==O VB@0:>=07>;C (37±17 ?@>B8 16±5 3>48=). 5<0T 4>ABC?=8E 40=8E I>4> 4>23>B@820;>3> 70AB>AC20==O VB@0:>=07>;C C ?0FVT=BV2, E2>@8E =0 F8@>7.

8@:>20 =54>AB0B=VABL: 4>ABC?=V >1<565=V 40=V I>4> 70AB>AC20==O ?5@>@0;L=>3> VB@0:>=07>;C ?0FVT=B0<8 7 ?>@CH5==O< DC=:FVW =8@>:!. ;V4 1CB8 >15@56=8<8 ?@8 70AB>AC20==V ?@5?0@0BC C FVTW :0B53>@VW ?0FVT=BV2.

\$0@<0F52B8G=V E0@0:B5@8AB8:8.

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 7 :@8H5G:>N @>652>3> :>;L>@C B0 :>@?CA> < :>@8G=52>3> :>;L>@C, I> ?5;5B8 2V4 1V;>3> 4> <0965 1V;>3> :>;L>@C.

"5@ABV.3 @>:8.

#<>28 715@V30==O.

15@V30B8 2 ACE>

15@V30B8 C =54>ABC?=>

#?0:>2:0.

> 4 :0?AC;8 C 1;VAB5@V. > 1 1;VAB5@C C :0@B>==V9 C?0:>2FV.

> 5 :0?AC; C 1;VAB5@V. > 3 01> 6 1;VAB5@V2 C :0@B>==V9 C?0:>2FV.

> 15 :0?AC; C 1;VAB5@V. > 1 01> 2 1;VAB5:@8 C :0@B>==V9 :>@>1FV.

0B53>@VO 2V4?CA:C. 0 @5F5?B>

8@>1=8:.

'!'"" .(.

VAF57=0E>465==O.

!0=:0;0@ >CW 81100 <. N7465, "C@5GG8=0.