

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

"

(LORATADINE)

!::04 ;V:0@AL:>3> 70A>1C:
4VNG0 @5G>28=0: loratadine;
1 B01;5B:0 @0B048=C 2 ?5@5@0EC20==V =0 100 % @5G>28=C (0,01 3) 10 <3;
4>?>28=8: :@>E<0;L :0@B>?;O=89, ;0:B>78 <=>3V4@0B, ?>2V4>=, :0;LFVN AB50@0B.

V:0@AL:0 D>@<0. "01;5B:8.

"01;5B:8 :@C3;>W D>@<8 1V;>3> :>;L>@C 7 ?;>A:>N ?>25@E=5N, 7 D0A:>N V @8A:>N 01> 157 @8A:8.

0720 B0 465==O 28@>1=8:0.

«\$0@<0:».

#:@0W=0, 04080, <. 8W2, 2C;.. \$@C=75, 63.

\$0@<0:>B5@0?52B8G=0 3@C?0.
=B83VAB018 4;O A8AB5<=>3> 70AB>AC20==O. >4 "I R06A X13.

>@0B048= B@8F8;;VG=89 0=B83VAB0N 0:B82=VABN 2V4=>A=> ?5@8D5@8G=8E 1-@5F5?B>@V2.

1V;LH>ABV ?0FVT=BV2 ?@8 70AB>AC20==V 2 @5:<5=4>20=V9 4>7V ;>@0B048= =5 G8=8BL
::V=VG=> 7=0GCI>W A540B82=>W B0 0=B8E>;V=5@3VG=>W 4VW. #?@>4>26 B@820;>3> ;V:C20==O =5
A?>AB5@V30;>AL ::V=VG=> 7=0GCI8E 7:07=8:0E 68BBT2>-206;828E DC=:FV9 >@30=V7@0B>@=8E
4>A;V465=L, DV7V:0;L=>3> >1AB565==O 01> 5;5:B@>:0@4V>3@0<8. >@0B048= =5 <0T 7=0GCI>3>
2?;82C =0 2-3VAB02V @5F5?B>@8. @5?0@0B =5 V=3V1CT 70E>?;5==O =>@5?V=5D@8=C V D0:B8G=> =5
<0T 2?;82C =0 DC=:FVN A5@F52>-AC48==>W A8AB5<8 01> =0 0:B82=VABL 2>4VO @8B

>A;V465==O 7 ?@>2545==O< H:V@=8E ?@>1 =0 3VAB0AC20==O @07>2>W 4>78 10 <3 ?>:070;8, I>
0=B83VAB048=8, 4>AO30T ?V:C G5@57 8-12 3>48= V B@820T 1V;LH5 24 3>48=. 5 2V47=0G0;>AO
@>728B:C B>;5@0=B=>ABV 4> 4VW ?@5?0@0BC ?VA;O 28 4=V2 70AB>AC20==O ;>@0B048=C.

;V=VG=0 5D5:B82=VABL V 157?5:0.

V;LH5 10000 ?0FVT=BV2 (2V:< 2V4 12 @>:V2) >B@8@0B048=< (B01;5B:8 ?> 10 <3) C :>=B@>;L>20=8E
::V=VG=8E 4>A;V465==OE. >@0B048= (B01;5B:8) 2 4>7V 10 <3 1 @07 =0 4>1C 1C2 5D5:B82=VH8<, =V6
?;0F51>, V B0:8< 65 5D5:B82=8<, O: ::5<0AB8=, 2V4=>A=> ?>:@0I5==O AB0=C ?@8 A8<0E (=070;L=8E V
=5 =070;L=8E) 0;5@3VG=>3> @8=VBC. # F8E 4>A;V465==OE A>;82VABL 28=8:0;0 7<5=H>N G0AB>B>N
?@8 70AB>AC20==V ;>@0B048=C, =V6 ::5<0AB8=C, V ?@0:B8G=> 7 B0:>N 6 G0AB>B>N, O: V ?@8
70AB>AC20==V B5@D5=048=C B0 ?;0F51>.

!5@54 CG0A=8:V2 F8E 4>A;V465=L (C 2VfV 2V4 12 @>:V2) 1000 ?0FVT=BV2 V7 E@>=VG=>N
V4V>?0B8G=>N :@>?82O=:>N 1C;8 70@5TAB@>20=V C ?;0F51>-:>=B@>;L>20=8E 4>A;V465==OE.
>@0B048= C 4>7V 10 <3 1 @07 =0 4>1C 1C2 5D5:B82=VH8< 70 ?;0F51> C ;V:C20==V E@>=VG=>W
V4V>?0B8G=>W :@>?82O=:>8, I> ?V4B25@46CTBLAO ?>A;01;5==O< A25@156C, 5@8B5<8 V

0;5@3VG=>3> 28A8?0==O. # F8E 4>A;V465==OE G0AB>B0 A>;82>ABV 1C;0 ?>4V1=>N ?@8
70AB>AC20==V ;>@0B048=0 B0 ?;0F51>.

VB8. ;87L:> 200 4VB59 (2V:< 2V4 6 4> 12 @>:V2) V7 A57>==8< 0;5@3VG=8< @8=VB<< >B@8@0B048=
(A8@>?) C 4>70E 4> 10 <3 1 @07 =0 4>1C 2 :=B@>;L>20=8E ;;V=VG=8E 4>A;V465==OE. V=H>
4>A;V465==V 60 4VB59 (C 2VfV 2V4 2 4> 5 @>:V2) >B@8@0B048= (A8@>?) C 4>7V 5 <3

1 @07 =0 4>1C. 5?5@5410G5=V ?>1VG=V @50:FVW =5 A?>AB5@V30;8AL. D5:B82=VABL C 4VB59 1C;0
>4V1=>N 5D5:B82=>ABV C 4>@>A;8E.

A<:BC20==O. >@0B048= H284:> V 4>1@5 2A<:BCTBLAO. 0AB>AC20==O ?@5?0@0BC ?V4 G0A W48
<>65 45I> 70B@8

>7?>4V.; >@0B048= 7207CTBLAO 0:B82=> (2V4 97 % 4> 99 %) 7 1V;;0<8 ?;07<8 :@>2V, 0 9>3> 0:B82=89
<5B01>;VB 7 ?>N 0:B82=VABN (2V4 73 % 4> 76 %). # 74>@>28E 4>1@>2>;LFV2 ?5@V>4
=0?V2@>7?>4V;C ;>@0B048=C B0 9>3> 0:B82=>3> <5B01>;VB0 2 ?;072V A;040T ?@81;87=> 1 B0

2 3>48=8 2V4?>2V4=>.

V>B@0=AD>@<0FVO. VA;O ?5@>@0;L=>3> 70AB>AC20==O ;>@0B048= H284:> V 4>1@5
01A>@1CTBLAO, 0 B0:>6 5:AB5=A82=> <5B01>;V7CTBLAO ?@8 ?5@H>E>465==V G5@57 ?5GV=:C,
3>;>2=8< G8=><, 70 4>?><>3>N CYP3A4 V CYP2D6. A=>2=89 <5B01>;VB 457;>@0B048= T D0@
<0>;>3VG=> 0:B82=8< V 1V;LH>NN 2V4?>2V40T 70 ;;V=VG=89 5D5:B. >@0B048= V 457;>@0B048=
4>AO30NBL <0:A8<0;L=>W :=F5=B@0FVW C ?;072V (Tmax) G5@57 1-1,5 3>48=8 V 1,5-3,7 3>48=
2V4?>2V4=>, ?VA;O 70AB>AC20==O ?@5?0@0BC.

82545==O. @81;87=> 40 % 4>78 282>48BLAO V7 A5G5N V 42 % 7 :0;< C?@>4>26 10 4=V2, 2 >A=>2=>
D>@ :=□N3>20=8E <5B01>;VBV2. @81;87=> 27 % 4>78 282>48BLAO V7 A5G5N C?@>4>26 ?5@H8E

24 3>48=. 5=H5 1 % 4VNG>W @5G>28=8 282>48BLAO C =57@@0B048= 01> 457;>@0B048=. # 4>@>A;8E
74>@>28E 4>1@>2>;LFV2 A5@54=V9 ?5@V>4 =0?V2282545==O ;>@0B048=C AB0=>282 8,4 3>48=8
(4V0?07>= 2V4 3 4> 20 3>48=), 0 >A=>2=>3> 0:B82=>3> <5B01>;VB0 28 3>48= (4V0?07>= 2V4 8,8 4> 92
3>48=).

>@CH5==O DC=:FVW =8@>:. # ?0FVT=BV2 V7 E@>=VG=8< ?>@CH5==O< DC=:FVW =8@>:
?V428IC20;8AO ?>:07=8:8 AUC V <0:A8<0;L=>W :=F5=B@0FVW C ?;072V (!max) ;>@0B048=C V 9>3>
0:B82=>3> <5B01>;VB0 ?>@V2=O=> 7 B0:8<8 ?>:07=8:0<8 2 ?0FVT=BV2 V7 =>@<0;L=>N DC=:FVTN
=8@>:. !5@54=V9 ?5@V>4 =0?V2282545==O ;>@0B048=C V 9>3> 0:B82=>3> <5B01>;VB0 =5
2V4@V7=O2AO 7=0G=>N N 2V4 ?>:07=8:V2 C 74>@>28E ;N459. # ?0FVT=BV2 V7 E@>=VG=8<
?>@CH5==O< DC=:FVW ?5GV=:8 35<>4V0;V7 =5 2?;820T =0 D0@<0>:V=5B8:C ;>@0B048=C V 9>3>
0:B82=>3> <5B01>;VB0.

>@CH5==O DC=:FVW ?5GV=:8. # ?0FVT=BV2 V7 E@>=VG=8< 0;:>3>;L=8< C@065==O< ?5GV=:8
?>:07=8:8 AUC V !max ;>@0B048=C 1C;8 2 420 @078 28I8<8, 0 WE 0:B82=>3> <5B01>;VBC =5 7B=> ?@8
?>@V2=O==V 7 B0:8<8 ?>:07=8:0<8 2 ?0FVT=BV2 V7 =>@<0;L=>N DC=:FVTN ?5GV=:8. 5@V>4
=0?V2282545==O ;>@0B048=C V 9>3> 0:B82=>3> <5B01>;VB0 AB0=>28BL 24 V 37 3>48= 2V4?>2V4=> V
71V;LHCTBLAO 70;56=> 2V4 BO6:>ABV 70E2>@N20==O ?5GV=:8.

0FVT=B8 ;VB=L>3> 2V:C. >:07=8:8 D0@<0>:V=5B8:8 ;>@0B048=C V 9>3> 0:B82=>3> <5B01>;VBC 1C;8
0=0;>3VG=8<8 2 74>@>28E 4>@>A;8E 4>1@>2>;LFV2 V 74>@>28E 4>1@>2>;LFV2 ;VB=L>3> 2V:C.

>:070==O 4;O 70AB>AC20==O.

!8<0B8G=5 ;V:C20==O E@>=VG=>W V4V>?0B8G=>W :@>?82O=:8 B0 0;5@3VG=>3> @8=VBC.

@>B8?>:070==O.

@5?0@0B ?@>B8?>:070=89 ?0FVT=B0< 7 ?V428I5=>N GCB;82VABN 4> 4VNG>W @5G>28=8 01> 4> 1C4L-O:>3> V=H>3> :=5=B0 ?@5?0@0BC.

A>1;82V 70AB5@565==O.

>@0B048= A;V4 7 >15@56=VABN 70AB>A>2C20B8 C ?0FVT=BV2 V7 BO6:>N D>@<>N ?>@CH5==O DC=:FVW ?5GV=:8.

> A:;04C ?@5?0@0BC 2E>48BL ;0:B>70. FVTW ?@8G8=8 ?0FVT=B8 7 B0:8<8 @V4:VA=8<8 A?04:>28<8 70E2>@N20==O<8 O: =5?5@5=>A878, 45DVF8B ;0:B078 0??0 V<0;L01A>@1FVO 3;N:>78-30;0:B>78 =5 ?>28==V 70AB>A>2C20B8 40=89 ?@5?0@0B.

0AB>AC20==O ?@5?0@0BC >@0B048= =5>1EV4=> ?@8?8=8B8 O:

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

03VB=VABL. 0=8E ?@> 70AB>AC20==O ;>@0B048=C 203VB=8<8 6V=:0<8 4C65 <0;>. >A;V465==O =0 B20@8=0E =5 28O28;8 ?@O<8E 01> =5?@O<8E =530B82=8E 5D5:BV2, I> AB>ACNBLAO

@5?@>4C:B82=>W B>:A8G=>ABV. 060=>, O: 70EV4 157?5:8, C=8:0B8 70AB>AC20==O ?@5?0@0BC >@0B048= C ?5@V>4 203VB=>ABV.

>4C20==O 3@C44N. \$V78:>-EV 282545==O ;>@0B048=C/<5B01>;VBV2 V7 3@C4=8< <>;>:>

\$5@B8;L=VABL. 0=V I>4> 2?;82C ;>@0B048=C =0 6V=>GC 01> G>;>2VGC D5@B8;L=VABL 2V4ACB=V.

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

030;>< ?@5?0@0B =5 2?;820T 01> 2?;820T =57=0G=8< G8=>< =0 H284:VABL @50:FVW ?@8 :5@C20==V 02B>B@0=A?>@B< 01> @>I>BV 7 V=H8<8 <5E0=V7<0<8.

@>B5 ?0FVT=B0 =5>1EV4=> ?@>V=D>@ 4C65 @V4:> ?>2V4><;O;>AO ?@> 28?04:8 A>=;82>ABV, O:V <>6CBL 2?;820B8 =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01> @>I>BC 7 V=H8<8 <5E0=V7<0<8.

VB8.

D5:B82=VABL B0 157?5:0 70AB>AC20==O ?@5?0@0BC 4VBO< 2V:>< 4> 2 @>:V2 =5 2AB0=>2;5=0.

@5?0@0B >@0B048=, B01;5B:8, ?@87=0G0B8 4VBO< 7 <0A>N BV;0 1V;LH5 30 :3.

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

5@>@0;L=>. "01;5B:8 <>6=0 70AB>A>2C20B8 =570;56=> 2V4 ?@89>

>@>A;8< B0 4VBO< 2V:>< 2V4 12 @>:V2 A;V4 ?@89<0B8 ?> 1 B01;5BFV (10 <3 ;>@0B048=C) 1 @07 =0 4>1C.

;O 4VB59 C 2VfV 2V4 2 4> 12 @>:V2 4>7C20==O 70;568BL 2V4 <0A8 BV;0. @8 <0AV BV;0 1V;LH5 30 :3:

10 <3 (1 B01;5B:0) 1 @07 =0 4>1C. VBO< 7 <0A>N BV;0 <5=H5 30 :3 70AB>A>2C20B8 ;>@0B048= C 283;04V A8@>?C.

0FVT=B8 ;VB=L>3> 2V:C. 5 28<030TBLAO :>@5:FVW 4>7C20==O ;N4O< ;VB=L>3> 2V:C.

0FVT=B8 7 ?>@CH5==O< DC=:FVW ?5GV=:8. 0FVT=B0< 7 ?>@CH5==O<8 DC=:FV9 ?5GV=:8 BO6:>3> ABC?5=O A;V4 ?@87=0G0B8 ?@5?0@0B C =86GV9 ?>G0B:>2V9 4>7V, >A:V;L:8 2 =8E<>6;825 7=865==O ;V@5=AC ;>@0B048=C. ;O 4>@>A;8E V 4VB59 V7 <0A>N BV;0 1V;LH5 30 :3 @5:><5=4>20=0 ?>G0B:>20 4>70 A;;040T 10<3 G5@57 45=L.

0FVT=B8 7 ?>@CH5==O< DC=:FVW =8@>:. 5<0T =5>1EV4=>ABV 2 :>@5:FVW 4>78 4;O ?0FVT=BV2 7 ?>@CH5==O< DC=:FVW =8@>:.

5@54>7C20==O.

5@54>7C20==O ;>@0B048=C ?V428ICT G0AB>BC 28=8:=5==O 0=B8E>;V=5@3VG=8E A87C20==V ?>2V4> <;O;>AO ?@> A>=;82VABL, B0EV:0@4VN V 3>;>2=89 1V;L. # @07V ?5@54>7C20==O @5:>5=4>20=> A8 <0B8G=5 B0 ?V4B@84>26 =5>1EV4=>3> ?5@V>4C G0AC. >6;825 70AB>AC20==O 0:B82>20=>3> 2C3V;;O

C 283;04V 2>4=>W ACA?5=7VW. "0:>6<>6=0 ?@>25AB8 ?@><820==O H;C=:0. >@0B048= =5 282>48BLAO V7 >@30=V72545==V 35<>4V0;V7C; 5D5:B82=VABL ?5@8B>=50;L=>3> 4V0;V7C C 282545==V ?@5?0@0BC =52V4><0. VA;O =52V4:;04=>W 4>?>>38 ?0FVT=B <0T 70;8H8B8AO ?V4 <548G=8< =03;04>

>1VG=V 5D5:B8.
I>:C VW A8AB5<8: 0=0DV;0:AVQ 2;;NG0NG8 0=3V>545
I>:C =5@2>2>W A8AB5<8: 70?0<>@>G5==O, A>;82VABL, 3>;>2=89 1V;L, =5@2>7=VABL, 157A>==O, AC4><8.
I>:C A5@F52>-AC48==>W A8AB5<8: B0EV:0@4VO, ?0;L?VB0FVO.
I>:C H;C=:>2>-:8H:>2>3> B@0:BC: =C4>B0, ACEVABL C @>BV, 30AB@8B.
I>:C 35?0B>1V;V0@=>W A8AB5<8: ?0B>;>3VG=V 7
I>:C H:V@8 B0 ?V4H:V@=>W ;:VB:>28=8: 28A8?0==O, 0;>?5FVO.
>@CH5==O 7030;L=>3> AB0=C V ?>2O70=V 7V A?>A>I>< 70AB>AC20==O ?@5?0@0BC: 2B><0, ?V428I5=89 0?5B8B.

70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.
@8 70AB>AC20==V >4=>G0A=> 7 0;:>3>;5< 5D5:B8 ;>@0B048=C =5 ?>A8;NNBLAO, I> ?V4B25@465=> 4>A;V465==O<8 ?A8E><>B>@=>W DC=:FVW.
>B5=FV9=0 270T<>4VO <>65 <0B8 AC20==V 2AVE 2V4>8E V=3V1VB>@V2 CYP3A4 01> CYP2D6, I> ?@872>48BL 4> ?V428I5==O @V2=V2 ;>@0B048=C, 0 F5 2 A2>N G5@3C <>65 1CB8 ?@8G8=>N ?V428I5==O G0AB>B8 28=8:=5==O ?>1VG=8E @50:FV9.
>2V4><;O;>AO ?@> ?V428I5==O :>=F5=B@0FV9 ;>@0B048=C 2 ?;072V ?VA;O >4=>G0A=>3> 70AB>AC20==O 7 :5B>:>=07>;<, 5@8B@>< V F8<5B848=><, I> =5 AC?@>2>46C20;>AO ;;V=VG=> 7=0GCI8<8 7

"5@ABV.3 @>:8.
5 70AB>A>2C20B8 ?@5?0@0B ?VA;O 70:V=G5==O B5@ABV, 707=0G5=>3> =0 C?0:>2FV.

#<>28 715@V30==O.
15@V30B8 2 ACE>
15@V30B8 C =54>ABC?=>.

#?0:>2:0.
> 10 B01;5B>: C 1;VAB5@V. >1 01> 2 1;VAB5@8, 2;;045=V C ?0G:C.

0B53>@VO 2V4?CA:C.
57 @5F5?B0.

!" #&/
>?> <548F8=A:>

"
(LORATADINE)

!>AB02 ;5:0@AB25==>3> A@54AB20:
459AB2CNI55 25I5AB2>: loratadine;
1 B01;5B:0 A>45@68B ;>@0B048=0 2 ?5@5AGQB5 =0 100 % 25I5AB2> (0,01 3) 10 <3;
2A?><>30B5;L=K5 25I5AB20: :@0E<0; :0@B>D5;L=K9, ;0:B>7K <=>384@0B, ?>284>=, :0;LF8O AB50@0B.

5:0@AB25==0O D>@<0. "01;5B:8.
"01;5B:8 :@C3;>9 D>@3> F25B0 A ?;>A:>9 ?>25@E=>ABLN, A D0A:>9 8 @8A:>9 8;8 157 @8A:8.

0720=85 8 <5AB>=0E>645=85 ?@>872>48B5;O.
«\$0@<0:».

#:@08=0, 04080, 3. 852, C;.. \$@C=75, 63.

\$0@<0:>B5@0?52B8G5c:0O 3@C??0. =B838AB0<8==K5 A@54AB20 4;O A8AB5<=>3> ?@8<5=5=8O.
>4 " ! R06A X13.

>@0B048= B@8F8;:8G5A:>5 0=B838AB0<8==>5 A@54AB2> A A5;5:B82=>9 0:B82=>ABLN 2 >B=>H5=88
?5@8D5@8G5A:8E 1-@5F5?B>@>2.

1>;LH8=AB20 ?0F85=B>2 ?@8 ?@8<5=5=88 2 @5:><5=4>20==>9 4>75 ;>@0B048= =5 >:07K205B
::8=8G5A:8 7=0G8<>3> A540B82=>3> 8 0=B8E>;8=5@38G5A:>3> 459AB28O. B5G5=85 4;8B5;L=>3>
;5G5=8O =5 =01;N40;>AL ::8=8G5A:8 7=0G8@0B048= =5 8<55B 7=0G8<>3> 2;8O=8O =0 2-38AB0<8=>2K5
@5F5?B>@K. @5?0@0B =5 8=3818@C5B 70E20B =>@M?8=5D@8=0 8 D0:B8G5A:8 =5 >:07K205B 2;8O=8O
=0 DC=:F8N A5@45G=>-A>AC48AB>9 A8AB5ABL 2>48B5;O @8B<0 A5@4F0.

AA;54>20=8O A ?@>2545=85< :>6=KE ?@>1 =0 38AB0<8= ?>A;5 ?@8<5=5=8O @07>2>9 4>7K 10 <3
?>:070;8, GB> 0=B838AB0<8==K9 MDD5:B 2>7=8:05B G5@57 1-3 G0A0, 4>AB8305B ?8:0 G5@57 8-12
G0A>2 8 4;8BAO 1>;55 24 G0A>2. 5 >B<5G0;>AL @0728B8O B>;5@0=B=>AB8 : 459AB28N ?@5?0@0B0
?>A;5 28 4=59 ?@8<5=5=8O ;>@0B048=0.

:8=8G5A:0O MDD5:B82=>ABL 8 157>?0A=>ABL.

>;55 10000 ?0F85=B>2 (2 2>7@0AB5 AB0@H5 12 ;5B) ?>;CG0;8 ;5G5=85 ;>@0B048=>< (B01;5B:8 ?> 10 <3) 2
:=B@>;8@C520=8OE. >@0B048= (B01;5B:8) 2 4>75 10 <3 1 @07 2 ACB:8 1K; 1>;55 MDD5:B82=K<, G5<
?;0F51>, 8 B0:8< 65 MDD5:B82=K<, :0: ::5<0AB8=, 2 >B=>H5=88 C;CGH5=8O A>AB>O=8O ?@8 A8<0E
(=070;L=KE 8 =5 =070;L=KE) 0;;5@38G5A:>3> @8=8B0. MB8E 8AA;54>20=8OE A>=;82>ABL 2>7=8:0;0 A
<5=LH59 G0AB>B>9 ?@8 ?@8<5=5=88 ;>@0B048=0, G5< ::5<0AB8=0, 8 ?@0:B8G5A:8 A B0:>9 65
G0AB>B>9, :0: 8 ?@8 ?@8<5=5=88 B5@D5=048=0 8 ?;0F51>.

!@548 CG0AB=8:>2 MB8E 8AA;54>20=89 (AB0@H5 12 ;5B) 1000 ?0F85=B>2 A E@>=8G5A:>9
848>?0B8G5A:>9 :@0?82=8F59 1K;8 70@538AB@8@>20=K 2 ?;0F51>-:=B@>;8@C520=8OE. >@0B048= 2
4>75 10 <3 1 @07 2 ACB:8 1K; 1>;55 MDD5:B82=K< G5< ?;0F51> 2 ;5G5=88 E@>=8G5A:>9 848>?0B8G5A:>9
:@0?82=8FK, GB> ?>4B25@6405BAO C<5=LH5=85< 7C40, M@8B59 AK?8. MB8E 8AA;54>20=8OE G0AB>B0
A>=;82>AB8 1K;0 ?>4>1=>9 ?@8 ?@8<5=5=88 ;>@0B048=0 8 ?;0F51>.

5B8. :>;> 200 45B59 (2 2>7@0AB5 >B 6 4> 12 ;5B) A A57>==K< 0;;5@38G5A:8< @8=8B<< ?>;CG0;8
;>@0B048= (A8@>?) 2 4>70E 4> 10 <3 1 @07 2 ACB:8 2 :=B@>;8@C520=8OE. 4@C3>< 8AA;54>20=88 60
45B59 (2 2>7@0AB5 >B 2 4> 5 ;5B) ?>;CG0;8 ;>@0B048= (A8@>?) 2 4>75 5 <3 1 @07 2 ACB:8.
5?@542845==K5 ?>1>G=K5 @50:F88 =5 =01;N40;8AL. -DD5:B82=>ABL C 45B59 1K;0 ?>4>1=>9
MDD5:B82=>AB8 C 27@>A;KE.

A0AK20=85. >@0B048= 1KAB@> 8 E>@>H> 2AKAK205BAO. @8<5=5=85 ?@5?0@0B0 2> 2@5

0A?@545;5=85. >@0B048= A2O7K205BAO 0:B82=> (>B 97 % 4> 99 %) A 15;:0<8 ?;0728, 0 53> 0:B82=K9
<5B01>;8B A C<5@5==>9 0:B82=>ABLN (>B 73 % 4> 76 %). # 74>@>2KE 4>1@>2>;LF52 ?5@8>4
?>;C@0A?@545;5=8O ;>@0B048=0 8 53> 0:B82=>3> <5B01>;8B0 2 ?;07<5 :@>28 A>AB02;O5B
?@81;878B5;L=> 1 8 2 G0A0 A>>B25BAB25==>.

8>B@0=AD>@<0F8O. >A;5 ?5@>@0;L=>3> ?@8<5=5=8O ;>@0B048= 1KAB@> 8 E>@>H>
01A>@18@C5BAO, 0 B0:65 M:AB5=A82=> <5B01>;878@C5BAO ?@8 ?5@2>< ?@>E>645=88 G5@57
?5G5=L, 3;02=K<>1@07><, A ?>>ILN CYP3A4 8 CYP2D6. A=>2=>9 <5B01>;8B 457;>@0B048= O2;O5BAO
D0@<0:>;>38G5A:8 0:B82=K< 8 2 1>;LH59 <5@5 >B25G05B 70 ::8=8G5A:89 MDD5:B. >@0B048= 8
457;>@0B048= 4>AB830NB <0:A8<0;L=>9 :=F5=B@0F88 2 ?;07<5 :@>28 (Tmax) G5@57 1-1,5 G0A0 8 1,5-
3,7 G0A0 A>>B25BAB25==>, ?>A;5 ?@8<5=5=8O ?@5?0@0B0.

K2545=85. @81;878B5;L=> 40 % 4>7K 2K2>48BAO A <>G>9 8 42 % A :0;< 2 B5G5=85 10 4=59, 2 >A=>2=><
2 D>@<5 :=JN38@>20==KE <5B01>;8B>2. @81;878B5;L=> 27 % 4>7K 2K2>48BAO A <>G>9 2 B5G5=85

?5@2KE 24 G0A>2. 5=55 1 % 459AB2CNI53> 25I5AB20 2K2>48BAO 2 =587<5=5==>9 0:B82=>9 D>@<5 :0;
G0A>2 (480?07>=>B 8,8 4> 92 G0A>2).

0@CH5=8O DC=:F88 ?>G5:.. # ?0F85=B>2 A E@>=8G5A:8< =0@CH5=85< DC=:F88 ?>G5: ?>2KH0;8AL
?>:070B5;8 AUC 8 <0:A8<0;L=>9 :>=F5=B@0F88 2 ?;07<5 :@>28 (!max) ;>@0B048=0 8 53> 0:B82=>3>
<5B01>;8B0 ?> A@02=5=8N A B0:8<8 ?>:070B5;O<8 C ?0F85=B>2 A =>@<0;L=>9 DC=:F859 ?>G5:.. !@54=89
?5@8>4 ?>;C2K2545=8O ;>@0B048=0 8 53> 0:B82=>3> <5B01>;8B0 =5 >B;8G0;AO 2 7=0G8B5;L=>9 <5@5 >B
?>:070B5;59 C 74>@>2KE ;N459. # ?0F85=B>2 A E@>=8G5A:8< =0@CH5=85< DC=:F88 ?5G5=8 35<>480;87
=5 2;8O5B =0 D0@<0:>:8=5B8:C ;>@0B048=0 8 53> 0:B82=>3> <5B01>;8B0.

0@CH5=8O DC=:F88 ?5G5=8. # ?0F85=B>2 A E@>=8G5A:8< 0;>3>;L=K< ?>@065=85< ?5G5=8 ?>:070B5;8
AUC 8 !max ;>@0B048=0 1K;8 2 420 @070 2KH5, 0 8E 0:B82=>3> <5B01>;8B0 =5 87<5=O;8AL ACI5AB25==>
?> A@02=5=8N A B0:8<8 ?>:070B5;O<8 C ?0F85=B>2 A =>@<0;L=>9 DC=:F859 ?5G5=8. 5@8>4
?>;C2K2545=8O ;>@0B048=0 8 53> 0:B82=>3> <5B01>;8B0 A>AB02;O5B 24 8 37 G0A>2 A>>B25BAB25==> 8
C25;8G8205BAO 2 7028A8<>AB8 >B BO65AB8 701>;520=8O ?5G5=8.

0F85=BK ?>68;>3> 2>7@0AB0. >:070B5;8 D0@<0:>:8=5B8:8 ;>@0B048=0 8 53> 0:B82=>3> <5B01>;8B0 1K;8
0=0;>38G=K<8 C 74>@>2KE 27@>A;KE 4>1@>2>;LF52 8 74>@>2KE 4>1@>2>;LF52 ?>68;>3> 2>7@0AB0.

>:070=8O : ?@8<5=5=8N.

!8<0B8G5A:>5 ;5G5=85 E@>=8G5A:>9 848>?0B8G5A:>9 :@0?82=8FK 8 0;;5@38G5A:>3> @8=8B0.

@>B82>?>:070=8O.

@5?0@0B ?@>B82>?>:070= ?0F85=B0< A ?>2KH5==>9 GC2AB28B5;L=>ABLN : 459AB2CNI5 4@C3>=5=BC
?@5?0@0B0.

A>1K5 ?@54>AB5@565=8O.

>@0B048= A;54C5B A >AB>@>6=>ABLN ?@8<5=OBL C ?0F85=B>2 A BO65;>9 D>@<>9 =0@CH5=8O
DC=:F88 ?5G5=8.

A>AB02 ?@5?0@0B0 2E>48B ;0:B>70. 0F85=BK A B0:8<8 @54:8<8 =0A;54AB25==K<8 701>;520=8O<8 :0:
=5?5@5=>A8<>ABL 30;0:B>7K, 45D8F8B ;0:B07K 0??0 8 <0;L01A>@1F8O 3;N:>7K-30;0:B>7K =5 4>;6=K
?@8<5=OBL 40==K9 ?@5?0@0B0.

@8<5=5=85 ?@5?0@0B0 >@0B048= =5>1E>48<> ?@5:@0B8BL :0: <8=8

@8<5=5=85 2 ?5@8>4 15@5<5==>AB8 8;8 :>@<;5=8O 3@C4LN.

5@5<5==>ABL. 0==KE > ?@8<5=5=88 ;>@0B048=0 15@5<5==K<8 65=I8=0<8 >G5=L <0;>. AA;54>20=8O =0
682>B=KE =5 2KO28;8 ?@02, :0A0NI8EAO @5?@>4C:B82=>9 B>:A8G=>AB8. 5;0B5;L=>, 2 :0G5AB25
<5@K 157>?0A=>AB8, 871530BL ?@8<5=5=8O ?@5?0@0B0 >@0B048= 2 ?5@8>4 15@5<5==>AB8.
>@<;5=85 3@C4LN. \$878:>-E8<8G5A:85 40==K5 A2845B5;LAB2CNB > 2K2545=88 ;>@0B048=0/
<5B01>;8B>2 A 3@C4=K< <>;>:A>;L:C @8A: 4;O @515=:0 =5 <>65B 1KBL 8A;;NG5=, ?@5?0@0B
>@0B048= =5 A;54C5B ?@8<5=OBL 2 ?5@8>4 :>@<;5=8O 3@C4LN.
\$5@B8;L=>ABL. 0==K5 >B=>A8B5;L=> 2;8O=8O ;>@0B048=0 =0 65=A:CN 8;8 D5@B8;L=>ABL
>BACBAB2CNB.

!/?>A>I=>ABL 2;8OBL =0 A:>@>ABL @50:F88 ?@8 C?@02;5=88 02B>B@0=A?>@B< 8;8 @01>B5 A 4@C38
<8 <5E0=87<0<8.

>1I5< ?@5?0@0B =5 2;8O5B 8;8 2;8O5B =57=0G8B5;L=K<>1@07<< =0 A:>@>ABL @50:F88 ?@8
C?@02;5=88 02B>B@0=A?>@B< 8;8 @01>B5 A 4@C38<8 <5E0=87<0<8.

"5<=5<5=55 ?0F85=B0=5>1E>48<> ?@>8=D>@<8@>20BL, GB> >G5=L @54:> A>>1I0;>AL> A;CG0OE
A>=;82>AB8, :>B>@K5 <>3CB 2;8OBL =0 A?>A>1=>ABL C?@02;OBL 02B>B@0=A?>@B× 8;8 @01>BC A
4@C38<8<5E0=87<0<8.

5B8.

-DD5:B82=>ABL 8 157>?0A=>ABL ?@8<5=5=8O ?@5?0@0B0 45BO< 4> 2 ;5B =5 CAB0=>2;5=0.
@5?0@0B >@0B048=, B01;5B:8, =07=0G0BL 45BO< A<0AA>9 B5;0 1>;55 30 :3.

!>A>1 ?@8<5=5=8O 8 4>7K.

5@>@0;L=>. "01;5B:8 <>6=> ?@8<5=OBL =57028A8<> >B ?@85<0 ?8I8.

7@>A;K< 8 45BO< AB0@H5 12 ;5B A;54C5B ?@8=8<0BL ?> 1 B01;5B:5 (10<3 ;>@0B048=0) 1 @07 2 ACB:8.
;O 45B59 >B 2 4> 12 ;5B 4>78@>2:0 7028A8B >B <0AAK B5;0. @8 <0AA5 B5;0 1>;55 30 :3: 10<3
(1 B01;5B:0) 1 @07 2 ACB:8. 5BO< A<0AA>9 B5;0 <5=55 30 :3 ?@8<5=OBL ;>@0B048= 2 2845 A8@>?0.
0F85=BK ?>68;>3> 2>7@0AB0. 5 B@51C5BAO :>@@5:F88 4>78@>2:8 ;N4O< ?>68;>3> 2>7@0AB0.
0F85=BK A =0@CH5=85< DC=:F88 ?5G5=8. 0F85=B0< A =0@CH5=8O<8 DC=:F89 ?5G5=8 BO65;>9
AB5?5=8 A;54C5B =07=0G0BL ?@5?0@0B 2 1>;55 =87:>9 =0G0;L=>9 4>75, ?>A>;;L:C C =8E 2>7<>6=>
A=865=85 ;;8@5=A0 ;>@0B048=0. ;O 27@>A;KE 8 45B59 A<0AA>9 B5;0 1>;55 30 :3 @5:><5=4>20==0O
=0G0;L=0O 4>70 A>AB02;O5B 10<3 G5@57 45=L.
0F85=BK A =0@CH5=85< DC=:F88 ?>G5:. 5B =5>1E>48<>AB8 2 :>@@5:F88 4>7K 4;O ?0F85=B>2 A
=0@CH5=85< DC=:F88 ?>G5:.

5@54>78@>2:0.

5@54>78@>2:0 ;>@0B048=0 ?>2KH05B G0AB>BC 2>7=8:=>25=8O 0=B8E>;8=5@38G5A:8E A8<>2. @8
?5@54>78@>2:5 A>>1I0;>AL> A>=;82>AB8, B0E8:0@488 8 3>;>2=>9 1>;8. @8 ?5@54>78@>2:5 @5:>
<5=4>20=> A8<0B8G5A:>5 8 ?>445@6820NI55 ;5G5=85 2 B5G5=85 =5>1E>48<>3> ?5@8>40 2@5<5=8. >7
<>6=> ?@8<5=5=85 0:B828@>20==>3> C3;O 2 2845 2>4=>9 ACA?5=788. "0:65 <>6=> ?@>25AB8 ?@>
@0B048= =5 2K2>48BAO 87 >@30=87<0 ?@8 ?@>2545=88 35<>480;870; MDD5:B82=>ABL
?5@8B>=50;L=>3> 480;870 2 2K2545=88 ?@5?0@0B0 =58725AB=0. >A;5 =5>B;>6=>9 ?><>I8 ?0F85=B 4>;65=
>AB020BLAO ?>4 <548F8=A:8< =01;N45=85

>1>G=K5 MDD5:BK.

!> AB>@>=K 8<9 A8AB50=0D8;0:A8O, 2;;NG0O 0=38>M45.

!> AB>@>=K =5@2=>9 A8AB5 3>;>2>:@C65=85, A>=;82>ABL, 3>;>2=0O 1>;L, =5@2>7=>ABL,
15AA>==8F0, AC4>@>38.

!> AB>@>=K A5@45G=>-A>AC48AB>9 A8AB5 B0E8:0@48O, ?0;L?8B0F8O.

!> AB>@>=K 65;C4>G=>-:8H5G=>3> B@0:B0: B>H=>B0, ACE>ABL 2> @BC, 30AB@8B.

!> AB>@>=K 35?0B>18;80@=>9 A8AB5<K: ?0B>;>38G5A:85 87<5=5=8O DC=:F88 ?5G5=8.

!> AB>@>=K :>68 8 ?>4:>6=>9 B:0=8: AK?L, 0>;?5F8O.

0@CH5=8O >1I53> A>AB>O=8O 8 A2O70==K5 A> A?>A>I>< ?@8<5=5=8O ?@5?0@0B0: CAB0;>ABL,
?>2KH5==K9 0??5B8B.

708<>459AB285 A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8 8 4@C385 284K 2708<>459AB289.

@8 ?@8<5=5=88 >4=>2@5<5==> A 0;;>3>;5< MDD5:BK ;>@0B048=0 =5 CA8;820NBAO, GB> ?>4B25@645=>
8AA;54>20=8O<8 ?A8E><>B>@=>9 DC=:F88.

>B5=F80;L=>5 2708<>459AB285 <>65B 8<5BL <5AB> ?@8 ?@8<5=5=88 2A5E 8725AB=KE 8=3818B>@>2
CYP3A4 8;8 CYP2D6, GB> ?@82>48B : ?>2KH5=8N C@>2=59 ;>@0B048=0, 0 MB> 2 A2>N>G5@54L <>65B
1KBL ?@8G8=>9 ?>2KH5=8O G0AB>BK 2>7=8:=>25=8O ?>1>G=KE @50:F89.

!>>1I0;>AL> ?>2KH5=88 :>=F5=B@0F89 ;>@0B048=0 2 ?;07<5 :@>28 ?>A;5 >4=>2@5<5==>3> ?@8<5=5=8O
A :5B>:>=07>;<, M@8B@><8F8=>< 8 F8<5B848=><, GB> =5 A>?@>2>640;>AL :;8=8G5A:8 7=0G8

!@>: 3>4=>AB8. 3 3>40.

5 ?@8<5=OBL ?@5?0@0B ?>A;5 >:>=G0=8O A@>:0 3>4=>AB8, C:070==>3> =0 C?0:>2:5.

#A;>28O E@0=5=8O.

%@0=8BL 2 ACE× <5AB5 ?@8 B525 °!.

%@0=8BL 2 =54>ABC?=>× 4;O 45B59 <5AB5.

#?0:>2:0.

> 10 B01;5B>: 2 1;8AB5@5. > 1 8;8 2 1;8AB5@0, 2;>65==K5 2 ?0G:C.

0B53>@8O >B?CA:0.

57 @5F5?B0.