

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

"®  
(NIMOTOP®)

!::04:

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

1 D;0:>= 50 <;

4>?>28=8: A?8@B 5B8;>289 96 %, <0:@>3>; 400, =0B@VN F8B@0B, :8A;>B0 ;8<>==0 1572>4=0, 2>40  
4;O V=T:FV9.

V:0@AL:0 D>@<0. >7G8= 4;O V=DC7V9.

A=>2=V DV78:>-EVABV: ?@>7>@89 7;53:0 6>2BC20B89 @>7G8=.

\$0@<0:>B5@0?52B8G=0 3@C?0. !5;5:B82=V 1;>:0B>@8 :0;LFVVT28E :0=0;V2 7 ?5@5206=8< 2?;82<< =0  
AC48=8.

>4 "% !08! □06.

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

\$0@<0:>48=0

5E0=V7< 4VW

V<>48?V= T 0=B03>=VAB× :0;LFVVT28E :0=0;V2 1,4-483V4@>?V@848=>2>W 3@C?8. # 7207:C V7  
28A>:N ;V?>DV;L=VABN @5G>28=0 4>1@5 ?@>=8:0T G5@57 35<0B>5=F5D0;VG=89 10@T@. # E>4V  
4>;V=VG=8E 4>A;V465=L 1C;> 2AB0=>2;5=>, I> =V<>48?V=, ?@>O2;ONG8 28A>:C 0DV==VABL V  
A5;5:B82=VABL, 7207CTBLAO V7 :0;LFVVT28-8 :0=0;0<8 Ca<sup>2+</sup> L-B8?C B0 1;>:CT B@0=A<5<1@0==5  
?@>=8:=5==O Ca<sup>2+</sup>. @8 ?0B>;>3VG=8E AB0=0E, ?>2O70=8E V7 ?V428I5=8< ?@>=8:=5==O< V>=V2 Ca<sup>2+</sup>  
4>=5@2>28E ;VB8=, =0?@8::04, ?@8 F5@51@0;L=V9 VH5 =V<>48?V= ?>:@0ICT WE AB01V;L=VABL  
B0 DC=:FV>=0;L=V 2;0AB82>ABV. H5=52@>;>3VG=V C@065==O C ?0FVT=V2 V7  
AC10@0E=>W40;L=8< :@>2>28;82<< B0 @V25=L A<5@B=>ABV ?@8 70AB>AC20==V =V<>48?V=C  
ACBBT2> 7=86CNBLAO.

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

1A>@1FVO

:B82=0 @5G>28=0 =V<>48?V= ?@0:B8G=> ?>2=VABN 2A<>:BCTBLAO ?@8 ?5@>@0;L=>  
70AB>AC20==V. 65 G5@57 10-15 E28;8= ?VA;O ?@89>20=>W D>@<8 ?@5?0@0BC 4VNG0 @5G>28=0  
C =572V. # >AV1 ;VB=L>3> 2V:C ?VA;O 1030B>@07>2>3> ?5@>@0;L=>3> 70AB>AC20==O  
?@5?0@0BC (30 <3 3 @078 =0 4>1C) A5@54=O ?V:>20 :=F5=B@0FVO C ?;072V (C<sub>max</sub>) AB0=>28BL  
7,343,2 =3/<; V 4>AO30TBLAO G5@57 0,6-1,6 3>48= (t<sub>max</sub>). # <>;>48E >AV1 ?VA;O >4=>:@0B=>3>  
?@89>7 ?@5?0@0BC ?> 30 <3 01> 60 <3 A5@54=O ?V:>20 :=F5=B@0FVO C ?;07:@>2V AB0=>28BL  
16±8 =3/<; B0 31±12 =3/<; 2V4?>2V4=>. V:>20 :=F5=B@0FVO C ?;0710 ?V4 :@82>N :=F5=B@0FVW  
(AUC) 7@>AB0T ?@>?>@FV9=> 4> 4>78 06 4> =0928I>W 4>A;V46C20=>W 4>78 (90 <3). @8  
4>7C20==V C 0,03 <3/:3/3>4 (157?5@5@2=0 V=DC7VO) 4>AO30TBLAO @V2=>206=0 :=F5=B@0FVO C  
?;072V, I> AB0=>28BL 17,6 26,6 =3/<;. VA;O 2=CB@VH=L>25==>W 1>;NA=>W V=T:FVW  
A?>AB5@V30;>AO 42>D07=5 7=865==O @V2=O :=F5=B@0FVW =V<>48?V=C C ?;072V V7 ?5@V>4>  
<=0?V2282545==O 5-10 E28;8= B0 1;87L:> 60 E28;8=.

>7@0E>20=89 >1T< @>7?>4V;C (V<sub>ss</sub>, 42>:=5=B=0 <>45;L) 4;O 2=CB@VH=L>25==>3> 22545==O  
4>@V2=NT 0,9-1,6 ;/:3 <0A8 BV;0. 030;L=89 (A8AB5<=89) ;;V@5=A AB0=>28BL 0,6-1,9 ;/3>4/:3.

2O7C20==O 7 1V::0<8 B0 @>7?>4V;

V<>48?V= =0 97-99 % 7207CTBLAO 7 1V::0<8 ?;07<8 :@>2V. # E>4V 4>;V=VG=8E 4>A;V465=L =V  
<>48?V= ?@>45<>=AB@C202 740B=VABL ?5@5B8=0B8 ?;0F5=B0@=89 10@ T@. 572060NG8 =0  
2V4ACB=VABL B0:8E 40=8E 4;O ;N48=8 <>6;825 ?@>=8:=5==O ?@5?0@0BC G5@57 35  
<0B>?;0F5=B0@=89 10@T@ C 6V=>:. # E>4V 4>;V=VG=8E 4>A;V465=L C <>;>FV 3>4CNG>W  
B20@8=8 1C;8 28O2;5=V 7=0G=> 28IV :=F5=B@0FVW =V<>48?V=C B0/01> 9>3> <5B01>;VBV2, =V6 C  
?;072V. # 3@C4=>2V.

VA;O ?5@>@0;L=>3> B0 2=CB@VH=L>25==>3> 22545==O =V<>48?V= <>6=0 28O28B8 C A?8==>  
<>7:>2V9 @V48=V C :>=F5=B@0FVW, O:0 AB0=>28BL 1;87L:> 0,5 % :>=F5=B@0FVW, 287=0G5=>W C  
?:072V. &5 T ?@81;87=> 5:2V20;5=B=8< :>=F5=B@0FVW =572 O70=>W @5G>28=8 C ?;072V.

5B01>;V7<, 282545==O B0 5:A:@5FVO

V<>48?V= <5B01>;V7CTBLAO G5@57 A8AB5E@>P4503A4, 3>;>2=8< G8=>< H;OE<<  
453V4@>35=V70FVW 483V4@>?V@848=>2>3> :V;LFO B0 >:8A;N20;L=>3> @>7I5?;5==O 5DV@C.  
:8A;N20;L=5 @>7I5?;5==O 5DV@C, 3V4@>:A8;N20==O 2- B0 6-<5B8;-3@C? B0 3;N:C@>=V70FVO O:  
@50:FVO :>=N30FVW T ?>40;LH8<8 206;828<8 ;0=:0<8 <5B01>;V7"@8 >A=>2=V <5B01>;VB8,  
287=0G5=V C ?;072V, =5 28O28;8 01> 28O28;8 ;8H5 =57=0G=C 70;8H:>2C B5@0?52B8G=C 0:B82=VABL.  
5 28O2;5=> V=4C:CNG>W 01> V=3V1CNG>W 0:B82=>ABV I>4> D5@<5=BV2 ?5GV=:8. 82545==O  
<5B01>;VBV2 C ;N48=8 74V9A=NTBLAO =0 50 % =8@:0<8 B0 =0 30 % G5@57 6>2G>282V4=V H;OE8.  
V=5B8:0 282545==O T ;V=V9=>N. 5@V>4 =0?V2282545==O =V<>48?V=C AB0=>28BL 2V4 1,1 4> 1,7  
3>48=8. "5@4 =0?V2282545==O 5-10 3>48= =5 T @5;520=B=8< 4;O 2AB0=>2;5==O V=B5@20;C <<< 4>7  
;V:0@AL:>3> 70A>1C.

15@54=O ?@>3@5AVO :>=F5=B@0FVW =V<>48?V=C C ?;072V ?VA;O ?5@>@0;L=>3> ?@89>n=24,  
>A>18 ;VB=L>3> 2V:C)

V>4>ABC?>=VABL

024O:8 V=B5=A82=>E>465==V G5@57 ?5GV=:C (?5@H5 ?@>E>465==O 1;87L:> 85-95 %) 01A>;NB=0  
1V>4>ABC?>=VABL AB0=>28BL 5-15 %.

0=V 4>;V=VG=8E 4>A;V465=L 7 157?5:8

0=V 4>;V=VG=8E 4>A;V465=L =5 28O28;8 A?5F8DVG=8E @878:V2 4;O ;N48=8 =0 ?V4AB02V  
AB0=40@B=8E 4>A;V465=L B>:A8G=>ABV >4=>@07>2>W B0 1030B>@07>28E 4>7,  
35=>B>:A8G=>ABV, :0=F5@>35==>3> ?>B5=V0;C B0 2?;82C =0 D5@B8;L=VABL C G>;>2V:V2 B0  
6V=>:.

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

**>:070==O.**

@>DV;0:B8:0 V ;V:C20==O VH5>3VG=8E @>7;04V2, >1C<>2;5=8E A?07<<< AC48= 3>;>2=>3> <>7:C  
?VA;O AC10@0E=>W40;L=>3> :@>2>28;82C 2=0A;V4>: @>7@82C 0=52@87<8.

**@>B8?>:070==O.**

=482V4C0;L=0 ?V428I5=0 GCB;82VABL 4> =V<>48?V=C 01> 4> 1C4L-O:>3> :>=5=B0 ?@5?0@0BC.

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

V:0@AL:V 70A>18, O:V 2?;820NBL =0 =V<>48?V=

\$.C>:A5B8=

4=>G0A=5 70AB>AC20==O =V<>48?V=C B0 0=B845?@5A0=BC D;C>:A5B8=C A?@8G8=OT  
71V;LH5==O :>=F5=B@0FVW =V<>48?V=C C ?;072V <0965 =0 50 % C @V2=>206=>:A5B8=C C ?;072V  
7=0G=> 7=86CTBLAO, B>4V O: 4VO 9>3> 0:B82=>3> <5B01>;VBC =>@D;C>:A5B8=C =5 774V;  
«A>1;82>ABV 70AB>AC20==O»).

>@B@8?B8;V=

4=>G0A=5 70AB>AC20==O =V<>48?V=C 7 =>@B@8?B8;V=< ?@872>48BL 4> =57=0G=>3> 7=865==O  
5:A?>78FVW =V<>48?V=C C @V2=>206=>=F5=B@0FVO =>@B@8?B8;V=C C ?;072V 70;8H0TBLAO =57  
N.

?;82 =V<>48?V=C =0 V=HV ;V:0@AL:V 70A>18

=B83V?5@B5=782=V 70A>18

V<>48?V= <>65 ?>A8;N20B8 3V?>B5=782=89 5D5:B B0:8E 0=B83V?5@B5=782=8E ?@5?0@0BV2 ?@8  
WE >4=>G0A=>

- 4VC@5B8:V2,

- β-1;>:0B>@V2,

- V=3V1VB>@V2 \$ (V=3V1VB>@V2 0=3V>B5=78=?5@5B2>@N20;L=>3> D5@<5=BC),

- A 1-0=B03>=VABV2,

- V=H8E 0=B03>=VABV2 :0;LFDVN,

- α-04@5=>1;>:0B>@V2,

- V=3V1VB>@V2 D>AD>4V5AB5@078-5,

- α-<5B8;4>?8.

4=0: O:I>=5<>6;82> C=8:=CB8 :<>1V=0FV9 B0:>3> B8?C, =5>1EV4=> C206=> AB568B8 70 AB0=<> ?0FVT=B0.

84>2C48=

# E>4V 4>A;V465=L =0 <02?0E 2AB0=>2;5=>, I> >4=>G0A=5 2=CB@VH=L>25==5 70AB>AC20==O =V <>48?V=C (C 283;04V 1>;NA=>W V=T:FVW) V 0=B8-?@5?0@0BC 784>2C48=C?@872>48BL 4> 7=0G=>3> 71V;LH5==O @V2=O 784>2C48=C C ?;072V (AUC) V 7=865==O >1T3> @>7?>4V;C V ;;V@5=AC.

@8 >4=>G0A=>25==>β-04@5=>1;>:0B>@0<8 <>6;825 270T<=5 ?V4A8;5==O =530B82=>3>

V=>B@>?=>3> 5D5:BC B0 =02VBL @>728B>: 70ABV9=>W A5@F52>W =54>AB0B=>ABV.

>B5= FV9=> =5D@>B>:A8G=V ;V:0@AL:V 70A>18

4=>G0A=0 B5@0?VO ?>B5=FV9=> =5D@>B>:A8G=8<8 ?@5?0@0B0<8 (=0?@8::04 03;V:>7840<8, F5D0;>A?>@8=0<8, DC@>A5<) 01> ;V:C20==O ?0FVT=BV2 V7 ?>@CH5=>N DC=:FVTN =8@>: <>65 28::8:0B8 ?>40;LH5 ?>3V@H5==O DC=:FVW =8@>:.. >4V1=5 ;V:C20==O A;V4 ?@>2>48B8 ?V4 @5B5;L=8 < :>=B@>;5< DC=:FVW =8@>:.. /:I> 28O2;5=> ?>3V@H5==O DC=:FVW =8@>:.. =5>1EV4=>

@>73;O=CB8 ?8B0==O ?@> ?@8?8=5==O B5@0?VW =V<>48?V=>< (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

V:0@AL:V 70A>18, =5AC3>;5<

=DC7V9=89 @>7G8= V<>B>?® 1□T<=8E % A?8@BC, =5>1EV4=> 2@0E>2C20B8 <>6;82C 270T<>4VN V7 ;V:0@AL:8<8 70A>10<8, =5AC(482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

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

5:<>5=4CTBLAO @5B5;L=89 <=>VB>@8=3 AB0=C ?0FVT=B0 ?@8 ?V428I5==V

2=CB@VH=L>G5@5?=>3> B8A:C 01> ?V428I5=>48 C B:0=8=0E 3>;>2=>3> <>7:C (35=5@0;V7>20=> ;>2=>3> <>7:C), E>G0 70AB>AC20==O =V<>48?V=C =5 0A>FV9>20=5 V7 ?V428I5==O<

2=CB@VH=L>G5@5?=>3> B8A:C.

0AB>AC20==O =V<>48?V=C ?>B@51CT >A>1;82>W >15@56=>ABV ?@8 0@B5@V0;L=V9

3V?>B5=7VW (@V25=L A8AB>;VG=>3> B8A:C<5=H5 100 << @B.AB.).

# ?0FVT=BV2 V7 =5AB01V;L=>N AB5=>:0@4VTN 01> ?@>BO3× ?5@H8E 4 B86=V2 ?VA;O @>728B:C 3>AB@>3> V=D0@:BC :0@40 ;V:0@ ?>28=5= @5B5;L=> 72060B8 A?V22V4=>H5==O ?>B5=FV9=>3> @878:C (=0?@8::04, 7=865=89 :>@>=0@=89 :@>2>BV: B0:0@4V0;L=0 VH5@8ABV 2V4 ?@87=0G5==O ?@5?0@0BC (=0?@8::04, ?>:@015==O <>7:>2>W ?5@DC7VW).

/:I> T =5>1EV4=VABL C >4=>G0A=>AC20==V 0=B83V?5@B5=782=8E ?@5?0@0BV2, V<>B>?®, @>7G8= 4;O V=DC7V9, A;V4 ?@87=0G0B8 BV;L:8 70 C<>28 ?@>2545==O @5B5;L=>3> <=>VB>@8=3C (482. @>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

4=>G0A=0 B5@0?VO ?>B5=FV9=> =5D@>B>:A8G=8<8 ?@5?0@0B0<8 (=0?@8::04 03;V:>7840<8, F5D0;>A?>@8=0<8, DC@>A5<) 01> ;V:C20==O ?0FVT=BV2 V7 ?>@CH5=>N DC=:FVTN =8@>: <>65 A?@8G8=8B8 ?>40;LH5 ?>3V@H5==O DC=:FVW =8@>:.. >4V1=5 ;V:C20==O A;V4 ?@>2>48B8 ?V4

@5B5;L=8< :>=B@>;5< DC=:FVW =8@>:.. /:I> 28O2;5=> ?>3V@H5==O DC=:FVW =8@>:.. =5>1EV4=>

@>73;O=CB8 ?8B0==O ?@> ?@8?8=5==O B5@0?VW =V<>48?V=>< (482. @>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»).

:B82=0 @5G>28=0 ?@5?0@0BC V<>B>?®, @>7G8= 4;O V=DC7V9, T 45I> D>B>GCB;82>N, B> A;V4 C=8:0B8 ?@O<>3> ?>?040==O A>=OG=>3> A2VB;0 ?@8 9>3> 70AB>AC20==V. 4=0: O:I> V<>B>?®,

@>7G8= 4;O V=DC7V9, 22>4OBL ?@8 @>7AVO=>HBCG=>A2VB;5==V, ?@>BO3× 10 3>48= A?5FV0;L=V 70E8A=V 70E>48 =5 ?>B@V1=V./:I> =5<>6;82> C=8:=CB8 ?>?040==O A>=OG=8E ?@>

<5=V2 ?V4 G0A V=DC7VW, A;V4 268B8 2V4?>2V4=8E 70AB5@56=8E 70E>4V2 (B0:8E O: 70E8AB V=DC7V9=>3> =0A>A0 B0 A8AB5<8 A2VB;>=5?@>=8=>N >13>@B:>N; 28:>@8AB0==O B>=>20=8E

A8AB5< 4;O V=DC7VW).

>?5@5465==O

&59 <548G=89 ?@5?0@0B 1□T<=8E % 5B0=>;C, B>1B>, 2V4?>2V4=> 4> V=AB@C:FVW, 4> 50 3 =0 4 >1>2C 4>7C (250 <; @>7G8=C 4;O V=DC7V9). 5>1EV4=> 4>B@815@56=>ABV C @07V ?@87=0G5==O ?@5?0@0BC ?0FVT=B0<, O:V AB@0640NBL =0 0;>3>;V7<, ?0FVT=B0< V7 ?>@CH5=8< <5B01>;V7<< 0;>3>;N, 203VB=8< B0 6V=:0<, O:V 3>4CNBL 3@C44N, 4VBO< B0 ?0FVT=B0<, O:V =0;560BL 4>

3@C?8 28A>:3> @878:C, B0:8< O: ?0FVT=B8 V7 70E2>@N20==O<8 ?5GV=:8 01> 7 5?V;5?AVTN.VO V=H8E ;V:0@AL:8E 70A>1V2 <>65 7<5=HC20B8AO 01> ?>A8;N20B8AO ?V4 2?;82>< 0;>3>;N (482.

@>74V; «70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9»). >6;825 7=865==O H284:>ABV @50:FVW ?V4 G0A :5@C20==O 02B>B@0=A?>@B<> 01> @>1>BV 7 V=H8<8 <5E0=V7<0 <8.

V:0@AL:89 70AV11 D;0:= (50 <; @>7G8=C) 01> 5,1 <<>;L (115<3) =0B@VN =0 250 <;. &V 40=V A;V4 2@0E>2C20B8 C @07V ?@87=0G5==O ?@5?0@0BC ?0FVT=B0<, O:V 4>B@8, I> ?5@5410G0T :>=B@>;L A?>6820==O =0B@VN (=87L:>=0B@VT20/ =87L:>A>;L>20 4VTB0).

V<>B>?®, @>7G8= 4;O V=DC7V9 F5 ?@>7>@89 @>7G8= 1;V4>-6>2B>3> :>;L>@C. \$;0:>=8 V7

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

03VB=VABL

5<0T 40=8E 2V4?>2V4=8E :>=B@>;L>20=8E ;:V=VG=8E 4>A;V465=L I>4> 70AB>AC20==O ?@5?0@0BC 203VB=8< 6V=:0 ?>B@V1=> 70AB>AC20B8 ?@5?0@0B V<>B>?® ?V4 G0A 203VB=>ABV, A;V4 @5B5;L=> 72068B8 :>@8ABL V ?>B5=V9=89 @878: 2V4 ?@89> 2V4 BO6:>ABV ;:V=VG=>W :0@B8=8.

>4C20==O 3@C44N

8O2;5=>, I> :>=F5=B@0FVO =V<>48?V=C B0 9>3> <5B01>;V BV2 C 3@C4=> <>;>FV 70 ?>@O4:>< 25;8G8= 2V4?>2V40T B0:V9 :>=F5=B@0FVW C ?;07 :@>2V <0B5@V. ">?V4 G0A 70AB>AC20==O ?@5?0@0BC A;V4 ?@8?8=8B8 3>4C20==O 3@C44N.

\$5@B8;L=VABL

# ?>>48=>:8E 28?04:0E 2 C<>20E 70?;V4=5==O in vitro 0=B03>=VAB8 :0;L FVN 0A>FVN20;8AO 7 >1>@>B=8<8 1V>EV@>B:>B@820;>

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

40B=VABL :5@C20B8 02B>B@0=A?>@B<> B0 ?@0FN20B8 7 V=H8<8 <5E0=V7<0<8 <>65 1CB8 ?>@CH5=0 C 7207:C V7 <>6;828< 28=8=:5==O< 70?0<>@>G5==O. @8 70AB>AC20==V V=DC7V9=>3> @>7G8=C V<>B>?® F59 D0:B>@ 70728G09 =5 <0T 7=0G5==O.

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

>7C20==O

C@A V=DC7V9=>W B5@0?VW @>7?>G8=0NBL V7 2=CB@VH=L>25==>3> 22545==O ?@5?0@0BC V <>B>?® C 4>7V 1 <3 =V<>48?V=C/(5 <; @>7G8=C 4;O V=DC7V9)/3>4 ?@>BO3<< ?5@H8E 2-E 3>48= (1;87L:> 15 3/:3/3>4).

0 C<>28 4>1@>W ?5@5=>A8<>ABV ?@5?0@0BC V ?@8 2V4ACB=>ABV 28@065=>W 0@B5@V0;L=>W 3V?>B5=7VW ?VA;O ?5@H8E 42>E 3>48= 22545==O 4>7C 71V;LHCNBL 4> 2<3 =V<>48?V=C/(10 <; @>7G8=C 4;O V=DC7V9)/3>4 (1;87L:> 30 4).

0FVT=B0< V7 <0A>N BV;0 7=0G=><5=H5 70 :3 V >A>10< V7 ;01V;L=8< 0@B5@V0;L=8< B8A:>< 22545==O ?@5?0@0BC A;V4 @>7?>G8=0B8 7 4>78 0,5 <3/(2,5 <; ?@5?0@0BC V<>B>?®, @>7G8=C 4;O V=DC7V9)/3>4.

2545==O 2 F8AB5@=8 3>;>2=>3> <>7:C.

# E>4V EV@C@3VG=>3> 2B@CG0==O A2V6>?@83>B>20=89 @>7G8= =V<>48?V=C (1 <; V=DC7V9=>3> @>7G8=C V<>B>?® V 19 <; @>7G8=C V=35@0), ?V4V3@VB89 4> B56=0 22>48B8 V=B@0F8AB5@=0;L=>. :070=89 @>7G8= =5>1EV4=> 28:>@8AB0B8 >4@07C ?VA;O ?@83>BC20==O. 0FVT=B0<, C O:8E A?>AB5@V30NBLAO AC?CB=V =51060=V @50:FVW,<>65 1CB8 ?>B@V1=5 7 <5=H5==O 4>78 01> ?@8?8=5==O ;V:C20==O.

# @07V 70AB>AC20==O 4;O >4=>G0A=>3> ;V:C20==O @07<< V7 ?@5?0@0B0<8, V=4C:CNG8<8 01> V=3V1CNG8<8 A8AB5E@>

0FVT=B8 V7 ?>@CH5==O< DC=:FVW ?5GV=:8

# @07V BO6:8E ?>@CH5=L DC=:FVW ?5GV=:8, >A>1;82> ?@8 F8@>7V ?5GV=:8, 1V>4>ABC?=VABL =V<>48?V=C <>65 ?V428IC20B8AO C 7207:C 7V 7=865==O< 5D5:BC ?5@H>3> ?@>E>465==O B0 7=865==O< <5B01>;VG=>3> ;:V@5=AC. VO ?@5?0@0BC B0 ?>1VG=V @50:FVW, =0?@8::;04 0@B5@V0;L=0 3V?>B5=7VO, C F8E ?0FVT=BV2 <>6CBL 1CB8 1V;LH 28@065=8<8.

# B0:8E 28?04:0E A;V4 7<5=H8B8 4>7C 01> C @07V =5>1EV4=>ABV @>73;O=CB8 ?8B0==O ?@>  
?@8?8=5==O ;V:C20==O.

!>AV1 B0 B@820;VABL 70AB>AC20==O

0FVT=B0<, O:8< >1T<=5 ?5@520=B065==O =51060=5 01> ?@>B8?>:070=5, ?@5?0@0B <>6=0 22>48B8  
G5@57 F5=B@0;L=C 25=C 70 4>?><>3>N :0B5B5@0 157 4>40B:>2>3> 22545==O AC?CB=L>3>  
@>7G8=C 4;O V=DC7V9.

>7G8= 4;O V=DC7V9 V<>B>?@ ?@87=0G0NBL C 283;04V B@820;>W 2=CB@VH=L>25==>W  
V=DC7VW G5@57 F5=B@0;L=89 :0B5B5@ V7 28:>@8AB0==O< V=DC7V9=>3> =0A>A0. !8AB5<8  
7T4=CNBLAO >4=0 7 >4=>N 70 4>?><>3>N B@8:0=0;L=>3> 1;>:0-;:0?0=0. >7G8= 4;O V=DC7V9 V  
<>B>?@ =5 @5:><5=4CTBLAO 22>48B8 2 ?0:5B 01> D;0:= V7 :>V=DC7V9=8< @>7G8=>< B0 =5 A;V4 7  
@5?0@0B <>6=0 22>48B8 @07>< 7 >4=8< V7 B0:8E @>7G8=V2: 5 % @>7G8=>< 3;N:>78, 0,9 %  
@>7G8=>< =0B@VN E;>@84C, @>7G8=>< V=35@0 ;0:B0BC, @>7G8=>< V=35@0 ;0:B0BC 7 <03=VT<,  
@>7G8=>< 45:AB@0=C 40, ?>;V (0-2-3V4@>:AV5BV;) :@>E<0;N 6 %, 0;L1C< ?;07<8 :@>2V 5 % 01>  
FV;L=>N :@>2N. 07CNG8AL =0 @57C;LB0B0E 4>A;V465=L, <0=VB>; B0:>6 <>6=0 22>48B8 C ?5@V>4  
4> 24 3>48= O :>V=DC7VN. !?V22V4=>H5==O V<>B>?@, @>7G8= 4;O V=DC7V9, B0 AC?CB=V9  
@>7G8= <0T AB0=>28B8 1:4.

@87=0G5==O ?@5?0@0BC V<>B>?@, @>7G8=C 4;O V=DC7V9, <>65 1CB8 ?@>4>265=> ?@>BO3<>  
0=5AB57VW, EV@C@3VG=>3> 2B@CG0==O B0 0=3V>3@0DVW.

@>DV;0:B8G=5 70AB>AC20==O

=CB@VH=L>25==C B5@0?VN =V<>48?V=>< A;V4 @>7?>G8=0B8 =5 ?V7=VH5 =V6 G5@57 4 4=V  
?VA;O :@>2>28;82C V ?@>4>26C20B8 ?@>BO3<> CAL>3> ?5@V>4C <0:A8<0;L=>3> @878:C  
@>728B:C 207>A?071B> 4> 10-14 4=O ?VA;O AC10@0E=>W40;L=>3> :@>2>28;82C.

!>I> C ?@>F5AV ?@>DV;0:B8G=>3> 70AB>AC20==O @>7G8=C V<>B>?@ ?@>2>48BLAO  
EV@C@3VG=5 ;V:C20==O :@>2>28;82C, 2=CB@VH=L>25==C B5@0?VN =V<>48?V=>< =5>1EV4=>  
?@>4>26C20B8 O:

VA;O 70:V=G5==O V=DC7V9=>W B5@0?VW ?@>BO3<> =0ABC?=8E 7 4=V2 01> 4>2H5 @5:>  
<5=4CTBLAO ?5@>@0;L=89 ?@89>< B01;5B>20=>W D>@<8 =V<>48?V=C C 4>7V 60 <3 6 @07V2 =0  
4>1C V7 4>B@8<0==O< V=B5@20;C <0<8 =5 <5=H5 4-E 3>48=.

"5@0?52B8G=5 70AB>AC20==O.

!>I> 265 =0O2=V VH5;>3VG=V ?>@CH5==O, A?@8G8=5=V 207>A?07<>< 2=0A;V4>:

AC10@0E=>W40;L=>3> :@>2>28;82C, V=DC7V9=C B5@0?VN ?>B@V1=> @>7?>G8=0B8 O:><>30  
@0=VH5 V ?@>2>48B8 ?@>BO3<> I>=09<5=H5 5 4=V2, 0;5 =5 1V;LH5 14 4=V2.

VA;O 70:V=G5==O V=DC7V9=>W B5@0?VW ?@>BO3<> =0ABC?=8E 7 4=V2 @5:><5=4CTBLAO  
?5@>@0;L=89 ?@89>< B01;5B>20=>W D>@<8 =V<>48?V=C C 4>7V 60 <3 6 @07V2 =0 4>1C V7 4>B@8  
<0==O< V=B5@20;C <0<8 =5 <5=H5 4-E 3>48=.

!>I> 2 ?@>F5AV B5@0?52B8G=>3> 70AB>AC20==O @>7G8=C V<>B>?@ ?@>2>48BLAO EV@C@3VG=5  
;V:C20==O :@>2>28;82C, 2=CB@VH=L>25==C B5@0?VN =V<>48?V=>< =5>1EV4=> ?@>4>26C20B8 O:

## **VB8.**

57?5:0 B0 5D5:B82=VABL 70AB>AC20==O ?@5?0@0BC V<>B>?@ 4;O ;V:C20==O 4VB59 (2V:>< 4> 18  
@>:V2) =5 2AB0=>2;5=V. A:V;L:8 =0 40=89<><5=B 4>A2V4 70AB>AC20==O =V<>48?V=C 4;O  
;V:C20==O 4VB59 T =54>AB0B=V<, ?@5?0@0B V<>B>?@ =5 ?@87=0G5=89 4;O ;V:C20==O ?0FVT=BV2  
FVTW 2V:>2>W 3@C?8.

**5@54>7C20==O.**

!8<8 V=B>:A8:0FVW: ?@8 3>AB@>7C20==V A?>AB5@V30NBLAO 28@065=0 0@B5@V0;L=0  
3V?>B5=7VO, B0EV:0@4VO 01> 1@048:0@4VO, =C4>B0, 0 C @07V ?5@>@0;L=>3> ?5@54>7C20==O  
@>7;048 7 1>:C H;C=:>2>-.8H:>2>3> B@0:BC V =C4>B0.

V:C20==O V=B>:A8:0FVW: ?@8 3>AB@>7C20==V @5:><5=4CTBLAO =5309=0 2V4. @8 ?@87=0G5==V  
5:AB@5=>W 4>?><>38 :5@CNBLAO A8<0<8. @8 ?5@>@0;L=>AC20==V =V<>48?V=C O: 5:AB@5=>W  
B5@0?VW @5:><5=4CTBLAO ?@><820==O H;C=:0 7 ?>40;LH8< 70AB>AC20==O< 0:B82>20=>3>  
2C3V;;O. @8 ?>40;LH>3> B8A:C 2=CB@VH=L>25==> 22>4OBL =>@04@5=0;V= 01> 4>?0B =52V4<>89,  
?@8 ;V:C20==V V=H8E ?>1VG=8E @50:FV9:5@CNBLAO =091V;LH 28@065=8<8 A8<0<8.

>1VG=V @50:FVW.

86G5 =02545=> ?5@5;V: ?>1VG=8E @50:FV9, 287=0G5=8E C E>4V ;;V=VG=8E 4>A;V465=L ?@8  
70AB>AC20==V =V<>48?V=C 70 ?>:070==O< AC10@0E=>W40;L=89 :@>2>28;82 2=0A;V4>: 0=52@87  
<8, O:V @>7?>4V;5=> 70 G0AB>B>N 73V4=> 7 :0B53>@VO<8 CIOMS III (?;0F51>-.>=B@>;L>20=V  
4>A;V465==O: =V<>48?V= N=703; ?;0F51> N=692; =5:>=B@>;L>20=V 4>A;V465==O: =V<>48?V= N  
=2496 70 AB0=>=0 31 A5@?>=O 2005 @.)

# <560E :>6=>W 3@C?8 2V4?>2V4=> 4> G0AB>B8 28=8:=5==O ?>1VG=V @50:FVW =02545=> 2  
?>@O4:C 7=865==O WE ABC?5=O BO6:>ABV. 5@5;VG5=V =86G5 ?>1VG=V @50:FVW @>7?>4V;5=V  
70 G0AB>B>N 28=8:=5==O 2V4?>2V4=> 4> B0:>W 3@040FVW: 4C65 G0ABV (≥1/10), G0ABV (≥1/100,  
<1/10), =5G0ABV (≥1/1000, <1/100), ?>>48=>:V (2V4 ≥1/10000 4> <1/1000), @V4:VA=V (<1/10000),  
G0AB>B0 =52V4><0 (=5<>6;82> 287=0G8B8 =0 >A=>2V =0O2=8E 40=8E).

'0AB>B0 ;0A8 A8AB5<>@30=V2	5G0ABV	>>48=>:V
1>:C A8AB5<8 :@>2>B2>@5==O B0 ;VW A8AB5<8	B@> <1>F8B>?5=VO	
1>:C VW A8AB5<8	0;5@3VG=0 @50:FVO, H:V@=89 28A8?	
1>:C =5@2>2>W A8AB5<8	3>;>2=89 1V;L	
1>:C A5@FO	B0EV:0@4VO	1@048:0@4VO
1>:C AC48=	3V?>B5=7VO, 207>48;0B0FVO	
1>:C H;C=:>2>-.8H:>2>3> B@0:BC	=C4>B0	:8H:>20 =5?@>EV4=VABL
1>:C ?5GV=:8 B0 6>2G>282V4=8E H;OEV2		B@0=78B>@=5 ?V428I5==O 0:B82=>ABV D5@<5=BV2 ?5GV=:8
>7;048 7030;L=>3> AB0=C B0 C		@50:FVW C

>2V4><;5==O ?@> ?V4>7@N20=V ?>1VG=V @50:FVW

>2V4><;5==O ?@> ?V4>7@N20=V ?>1VG=V @50:FVW ?VA;O @5TAB@0FVW ;V:0@AL:>3> 70A>1C T  
206;828<8. >=8 40NBL 7<>3C ?@>2>48B8 157?5@5@2=89 <>=VB>@8=3 A?V22V4=>H5==O :>@8ABL  
/@878: I>4> ?@5?0@0BC. 548G=V ?@0FV2=8:8 ?>28==V ?>2V4><;OB8 ?@> 1C4L-O:V ?V4>7@N20=V  
?>1VG=V @50:FVW.

"5@ABV.4 @>:8.

#<>28 715@V30==O.

15@V30B8 ?@8 B5 ! 2>@83V=0;L=V9 C?0:>2FV 4;O 70E8ABC 2V4 A2VB;0, C =54>ABC?=>

5AC

V<>48?V=, 0:B82=0 @5G>28=0 V=DC7V9=>3> @>7G8=C V<>B>?®, 01A>@1CTBLAO  
?>;V2V=V;E;>@84<, B>3> 22545==O ?@5?0@0BC V<>B>?® =5>1EV4=> 28:>@8AB>2C20B8 BV;L:8  
A8AB5<8 7 ?>;V5B8;5=>28<8 B@C1:0<8.  
>7G8= 4;O V=DC7V9 V<>B>?® =5 @5:><5=4CTBLAO 22>48B8 2 ?0:5B 01> D;0:>= V7 :>V=DC7V9=8<  
@>7G8=>< B0 =5 A;V4 7

#?0:>2:0.

> 50 <; C D;0:>=V; ?> 1 D;0:>=C @07>< 7 ?>;V5B8;5=>2>N A?>;CG=>N B@C1:>N 4;O V=DC7<0B0 C  
:0@B>==V9 :>@>1FV, ?> 5 :>@>1>: 2 C?0:>2FV 7 ?>;V5B8;5=C.

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

0 @5F5?B>

**8@>1=8:.**

09T@ \$0@<0 , V<5GG8=0 / Bayer Pharma AG, Germany.

**VAF57=0E>465==O 28@>1=8:0 B0 9>3> 04@5A020465==O 4VO;L=>ABV.**

0975@-□V;L35;L/

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