

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

!;:04:

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

1 :0?AC;0 78=C 3V4@>E;>@84C 0,4 <3;

4>?>28=8: F5;N;>70 :@8AB0;VG=0, <03=VN AB50@0B, 48A?5@AVO<5B0:@8;0B=>3> A>?>;V<5@C (48A?5@AVO :>?>;V<5@C <5B0:@8;>2>W :8A;>B8 B0 5B8;0:@8;0BC (1:1) (30 %), =0B@VN 3V4@>:A84, B@80F5B8=, B0;L:, B8B0=C 4V>:A8= (171).

V:0@AL:0 D>@<0. 0?AC;8.

\$0@<0:>B5@0?52B8G=0 3@C?0. 0A>18, I> 70AB>A>2CNBLAO ?@8 4>1@>O:VA=V9 3V?5@?;07VW ?5@542>W 70;>78. =B03>=VAB8 α-
04@5=5@3VG=8E @5F5?B>@V2.
>4 "I G04C A02.

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

>:070==O. V:C20==O DC=:FV>=0;L=8E @>7;04V2 7 1>:C =86=VE A5G>282V4=8E H;OEV2 ?@84>1@>O:VA=V9 3V?5@?;07VW ?@>AB0B8.

@>B8?>:070==O.

50:FVW 3V?5@GCB;82>ABV, 2:;NG0NG8 0=3V>=52@>B8G=89 =01@O: 2V=:5, 4> B078=C 3V4@>E;>@84C 01> 4> 1C4L-O:>W 7 4>?>28=;
>@B>AB0B8G=0 3V?>B5=7VO; 28@065=0 ?5GV=:>20 =54>AB0B=VABL.

!?!>AVI 70AB>AC20==O B0 4>78. □>@>A;8< ?@89<0B8 ?> 1 :0?AC;V 1 @07 =0 4>1C 2 >48= V B>9 65 G0A ?VA;O ?@89>2B0B8 FV;>N, =5
@>76>2CNG8, 70?820NG8 1 A:;O=:>N 2>48.

"@820;VABL ;V:C20==O 2AB0=>2;NTBLAO V=482V4C0;L=>.

>@CH5==O DC=:FVW =8@>: =5 28<030T 7=865==O 4>7C20==O.

0FVT=B8 7 ?>@CH5==O< DC=:FVW ?5GV=:8 ;53:>3> B0 A5@54=L>3> ABC?5=O B06:>ABV B0:>6 =5 ?>B@51CNBL 7=865==O 4>7C20==O.

>1VG=V @50:FVW.

'0ABV ?>1VG=V 5D5:B8 (>1/100, <1/10)

>7;048 7 1>:C &! : 70?0<>@>G5==O.

1>:C AB0B52>W A8AB5<8: @5B@>3@04=0 5O:C;OFVO.

5G0ABV (>1/1000, <1/100)

>7;048 7 1>:C &! : 3>;>2=89 1V;L.

>7;048 7 1>:C A5@F52>-AC48==>W A8AB5<8: 2V4GCBBO A5@F518BBO, ?>ABC@0;L=0 3V?>B5=7VO.

5A?V@0B>@=>-<54V0AB8=0;L=V @>7;048: @8=VB.

>7;048 7 1>:C H;C=:>2>-:8H:>2>3> B@0:BC: 70?>@, 4V0@50, =C4>B0, 1;N20==O.

>7;048 7 1>:C H:V@8 B0 A;87>28E >1>;>=>:: 28A8?, :@>?82 O=;0, A25@1V6.

>7;048 7030;L=>3> E0@0:B5@C: 0AB5=VO.

V4:V (>1/10000, <1/1000)

>7;048 7 1>:C &!:=5?@8B><=VABL.

>7;048 7 1>:C H:V@8 B0 A;87>28E >1>;>=>:: 0=3V>=52@>B8G=89 =01@O: 2V=:5.

C65 @V4:V (<1/10000)

1>:C AB0B52>W A8AB5<8: ?@V0?V7

0E2>@N20==O H:V@8 B0 ?V4H:V@=>W ;:VB:>28=8: C8=4@<< !BV25=A0-6=>A>=0.

A=CNBL A?>=B0==V ?>2V4<<;5==O ?@> 28?04:8 0B@V0;L=>W DV1@8;OFVW, 0@8B5 C ?>AB@5TAB@0FV9=>4V, G0AB>B0 ?>2V4<<;5=L B0 @>;L B078=C C FL>

?8A0=V 28?04:8 V=B@0>?5@0FV9=>W =5AB01V;L=>ABV @094C6=>W >1>;>=:8 >:0 (A8=4@<< 72C65=>W 7V=8FV) ?@8 >?5@0FVW 7 ?@82>4C :0B0@0:B8 V 3;0C:><8 C ?0FVT=BV2, O:V B@820;89 G0A ?@89<0;8 B078= (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

5@54>7C20==O. # 28?04:C @V7:>3> 7=865==O B8A:C 2=0A;V4>: ?5@54>7C20==O A;V4 ?@>2>48B8 ?V4B@8: 28A>:>3> ABC?5=O 72O7C20==O B0 78=C 7 1V;:0<8 ?;07<8 ?@>2545==O 35<>4V0;V7C T=02@O4 G8 4>FV;L=8

<5B>N ?@8?8=5==O ?>40;LH>3> 2A<>:BC20==O ?@5?0@0BC <>6=0 HBCG=> 28;;8:0B8 1;N20==O. @8 ?5@54>7C20==V 7=0G=>W :V;L:>ABV ?@5?0@0BC ?0FVT=BC =5>1EV4=> ?@><8B8 H;C=>: V7 70AB>AC20==O< 0:B82>20=>3> 2C3V;;O B0 =87L:>>A<>B8G=8E ?>A;01;NNG8E 70A>1V2, B0:8E O: AC;LD0B =0B@VN.

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

0=89 ?@5?0@0B 70AB>A>2CNBL ;8H5 4;O ;V:C20==O G>;>2V:V2.

VB8. @5?0@0B =5 70AB>A>2CNBL 4VBO

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

5AB01V;L=VABL @094C6=>W >1>;>=:8 >:0 (A8=4@<< 72C65=>W 7V=8FV) ?>2O70=0 7 1;:>:C20==O< α₁-@5F5?>B@V2 ?V4 G0A EV@C@3VG=>3> 2B@CG0==O 7 ?@82>4C 2840;5==O :0B0@0:B8 V 3;0C:><8 2V47=0G0;0AL C 45O:8E ?0FVT=BV2, O:V ?@89<0;8 01> ?@89<0NBL B078=. FVTW ?@8G8=8 ?0FVT=B0<, O:8< 70?;0=>20=0 ??5@0FVO 7 2840;5==O :0B0@0:B8 V 3;0C:><8, =5 @5:><5=4CTBLAO ?@87=0G0B8 B078=.

/: ?@028;>, 70 1-2 B86=V ?5@54 ?@>2545==O< >?5@0FVW 7 ?@82>4C 2840;5==O :0B0@0:B8 V 3;0C:><8 @5:><5=4CTBLAO ?@8?8=8B8 ;V:C20==O B078=>B5 4>FV;L=VABL B0 B5@78=><=0 AL>3>4=VH=V9 45=L B>G=>=5 2AB0=>2;5=V.

@8 ?V43>B>2FV 4> ??5@0FVW EV@C@38->DB0;L<>;>38 <0NBL 4V7=0B8AO, G8 ?@89<02 (01> ?@89<0T) ?0FVT=B B078= 7 <5B>N ?>?5@5465==O <>6;828E CA::04=5=L, ?>2O70=8E 7 =5AB01V;L=VABN @094C6=>W >1>;>=:8 >:0.

/: V ?@8 70AB>AC20==V V=H8E α₁-04@5=>1;:>:0B>@V2, 2 >:@5<8E 28?04:0E ?@8 70AB>AC20==V <=V:0:0A <>6;825 7=865==O 0@B5@V0;L=>3> B8A:C, I> <>65 V=>4V ?@8725AB8 4> 2B@0B8 A2V4<<>ABV. @8 ?>O2V ?5@H8E >7=0: >@B>AB0B8G=>W 3V?>B5=7VW (70?0<>@>G5==O, A;01:VABL) ?0FVT=B<0T ?@89=0B8 3>@87>=B0;L=5 ?>;>65==O 4> 7=8:=5==O 281573040=8E A8

5@54 B8< O: @>7?>G0B8 ;V:C20==O ?@5?0@0B< 0=>?@>AB, A;V4 ?@>9B8 <548G=5 >1AB565==O 7 <5B>N 28O2;5==O V=H8E AC?CB=VE
70E2>@N20=L, I> <>6CBL A?@8G8=8B8 B0:V6 A02>W 70;>78. 5@54 ?>G0B:>< ;V:C20==O =5>1EV4=> ?@>25AB8 @5:B0;L=5 >1AB565==O ?5@54
2>W 70;>78 B0 ?@8 =5>1EV4=>ABV B5AB =0 287=0G5==O @V2=O A?5F8DVG=>3> 0=B835=C ?5@542>W 70;>78 (PSA) 4> ?>G0B:C B0 G5@57
>4=0:>2V ?@>

@87=0G0B8 ?@5?0@0B ?0FVT=B0< 7 BO6:>N D>@<>N =8@:>2>W =54>AB0B=>ABV (:;V@5=A :@50B8=V=C <10< ;/E2) =5>1EV4=> 7 >A>1;82>N
>15@56=VABN, >A:V;L:8 ;;V=VG=8E 4>A;V465=L 7 28:>@8AB0==O 0=>?@>AB C B0:8E ?0FVT=V2 =5 ?@>2>48;>AO.
=>4V <>6;82> 7=09B8 70;8H:8 B01;5B:8 C D5:0;VOE.

"078=C 3V4@>E;>@84 =5 A;V4 ?@87=0G0B8 C :<1V=0FVW 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 ?0FVT=B0< 7 =87L:8< <5B01>;V7<<< CYP2D6.
"078=C 3V4@>E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN C ?>T4=0==V 7 A8;L=8<8 V ?>□70T<>4VO 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0
V=HV 2848 270T<>4V9).

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.

>A;V465==O 2?;82C ?@5?0@0BC =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01> ?@0FN20B8 7 <5E0=V7<0<8 =5 ?@>2>48;8AO. 4=0: ?0FVT=B8
<0NBL 1CB8 ?>?5@5465=V ?@> <>6;82VABL 28=8:=5==O 70?0<>@>G5==O.

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

@8 >4=>G0A=>AC20==V B078=C 3V4@>E;>@84C 7 0B5=>;;><, 5=0;0?@8;>, =VD548?V=>< 01> B5>DV;V=>< ;V:0@AL:>W 270T<>4VW =5
2V47=0G0;>AO. 4=>G0A=5 70AB>AC20==O 7 F8<5B848=>< ?V428ICT, 0 7 DC@>A5< 7=86CT :>=F5=B@0FVN B078=C 2 ?;072V, 0;5 >A:V;L:8 FV
@V2=V 70;8H0NBLAO 2 <560E =>@<8, C A?5FV0;L=V9 :>@5:FVW 4>7C20==O B078=C =5<0T ?>B@518.
4>A;V465==OE in vitro 4V075?0<, ?@>?@0=>;>;, B@8E;>@<5BV0784, E;>@<048=>=, 078=C 2 ?;072V ;N48=8. >4V1=8< G8=>< B078= =5 ??0=>;>;C,
B@8E;>@<5BV0784C B0 E;>@<048=>=C 2 ?;072V ;N48=8.
4=>G0A=5 70AB>AC20==O B078=C 3V4@>E;>@84C 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 <>65 ?@8725AB8 4> 71V;LH5==O 2?;82C B078=C
3V4@>E;>@84C. !?V;L=5 70AB>AC20==O 7 :5B>:>=07>;< (2V4<<89 A8;L=89 V=3V1VB>@ CYP3A4) ?@872>48;> 4> 71V;LH5==O !max V AUC 4> 2,2
V 2,8 2V4?>2V4=>.

4=>G0A=5 70AB>AC20==O B078=C 3V4@>E;>@84C V ?0@>:A5B8=C (A8;L=89 V=3V1VB>@ !YP2D6) ?@872>48BL 4> 71V;LH5==O !max V AUC 4>
1,3 V 1,6 2V4?>2V4=>, 0;5 F5 =5 T ;;V=VG=> 7=0GCI8

"078=C 3V4@>E;>@84 =5 A;V4 ?@87=0G0B8 C :<1V=0FVW 7 A8;L=8<8 V=3V1VB>@0<8 CYP3A4 C ?0FVT=V2 7 =87L:8< <5B01>;V7<<< CYP2D6.

"078=C 3V4@>E;>@84 A;V4 70AB>A>2C20B8 7 >15@56=VABN C ?>T4=0==V 7 A8;L=8<8 V ?>

4=>G0A=5 70AB>AC20==O 7 V=H8<8 α_1 -04@5=>1;>;0B>@0<8 <>65 ?>A8;N20B8 3V?>B5=782=89 5D5:B.

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

$\$0@<0:>48=0 0=>?@>AB 281V@:>2> V :>=:C@5=B=> 1;>;CT ?>ABA8=0?B8G=V$ α_1 -04@5=>@5F5?B>@8, 7>:@5<0 α_1A B0 α_1D , I>
7=0E>4OBLAO C 3;04:V9 2>W 70;>78, H89:8 A5G>2>3> AB0B8G=>W G0AB8=8 C@5B@8. &5 ?@872>48BL 4> 7=865==O B>=CAC 3;04:>W 2>W
70;>78, H89:8 A5G>2>3> AB0B8G=>W G0AB8=8 C@5B@8 B0 ?>;V?H5==O 284V;5==O A5GV.

4=>G0A=> 7<5=HCNBLAO A8<8 >1AB@C:FVW B0 ?>4@07=5==O, ?>2O70=V 7 4>1@>O:VA=>N 3V?5@?;07VTN ?5@542>W 70;>78 (CB@C4=5==O
?>G0B:C A5G>28?CA:0==O, ?>A;01;5==O AB@C<5=O A5GV, :@0?0==O ?VA;O 70:V=G5==O A5G>28?CA:0==O, 2V4GCBBO =5?>2=>3> A?>@>6=5==O
A5G>2>3> 7828 4> A5G>28?CA:0==O, ?>7828 4> A5G>28?CA:0==O 2 =VG=89 G0A, =52V4;:04=VABL A5G>28?CA:0==O).

40B=VABL α_{1A} -04@5=>1;>:0B>@V2 7<5=HC20B8 0@B5@V0;L=89 B8A: ?>2O70=0 7V 7<5=H5==O< ?5@8D5@V9=>3> >?>@C. 0=>?@>AB C 4>1>2V9 4>7V 0,4 <3 =5 A?@8G8=OT ::V=VG=> 7=0GCI5 7=865==O A8AB5<=>3> 0@B5@V0;L=>3> B8A:C (") O: C E2>@8E =0 0@B5@V0;L=C 3V?5@B5=7VN, B0: V C ?0FVT=BV2 7 =>@<0;L=8< ?>G0B:>28< ".

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

IA>@IFVO. 0=>?@>AB O2;OT A>1>N B01;5B:C ?@>;=>3>20=>W 4VW 7 :>=B@>;L>20=8< 282V;L=5==O< =0 >A=>2V <0B@8:AC 7 28:>@8AB0==O< 35;N =5V>==>3> B8?C. \$>@<0 :0AC 70157?5GCT B@820;5 B0 ?>2V;L=5 282V;L=5==O B078=C, I> 40T 5:A?>78FVN 7V A;01:8<8 :>;820==O<8 ?@>BO3> < 24 3>48=. VA;O ?5@>@0;L=>3> ?@89>78=C 01A>@1CTBLAO 2 :8H5G=8:C. (284:VABL V @>7@1FVW =5 70;560BL 2V4 ?@89<0==O W6V.

"078= 45<>=AB@CT ;V=V9=C D0@<0:>:V=5B8:C. VA;O >4=>@07>2>3> ?@89>?@>ABC =0BI5 <0:A8<0;L=0 :>=F5=B@0FVO 0:B82=>W @5G>28=8 C ?;07AB5@V30TBLAO G5@57 6 3>48=. # @V2=>206=>AO30TBLAO =0 G5B25@B89 45=L ?@89>=F5=B@0FVW A?>AB5@V30TBLAO G5@57 4-6 3>48= =570;56=> 2V4 ?@89<0==O W6V. V: :>=F5=B@0FVW C ?;0711 =3/<; C @V2=>206=>

/: @57C;LB0B B@820;>3> 282V;L=5==O, =09=86G89 @V25=L :>=F5=B@0FVW B078=C C ?;0728BL 40 % <0:A8<0;L=>W :>=F5=B@0FVW =570;56=> 2V4 ?@89<0==O W6V.

>7?>4V;. 2O7C20==O 7 1V;;0<8 ?;07<8 99 %. 1T< @>7?>4V;5==O =57=0G=89 4> 0,2 ;/:3.

5B01>;V7"078=C 3V4@>E;>@84 =5 ?V440TBLAO 5D5:BC ?5@H>3> ?@>E>465==O V ?>2V;L=> <5B01>;V7CTBLAO 2 ?5GV=FV 7 CB2>@5==O< D0@ <0:>;>3VG=> 0:B82=8E <5B01>;V BV2, I> 715@V30NBL 28A>:C A5;5:B82=VABL 4> 0;LD0-04@5=>@5F5?B>@V2. V;LH0 G0AB8=0 0:B82=>W @5G>28=8 ?@8ACB=O 2 :@>2V C =57

82545==O. "078=C 3V4@>E;>@84 282>48BLAO =8@:0<8, 4-6 % 4>78 284V;OTBLAO C =574 =0?V2282545==O B078=C ?@8 >4=>@07>2>206=>48=, 2V4?>2V4=>.

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

A=>2=V DV78:>-EVABV: B25@4V 65;0B8=>2V :0?AC;8 7 :>2?0G:< :>@8G=52>3> :>;L>@C V :>@?CA<< ?><0@0=G52>3> :>;L>@C, @>73> 01> <0965 1V;>3> :>;L>@C 3@0=C;L>20=89 <0B5@V0;.

"5@ABV.

24

#<>28 715@V30==O.

15@V30B8 2 ACE>

15@V30B8 2 =54>ABC?=>

#?0:>2:0.

> 10 :0?AC; C 1;VAB5@V; ?> 3 1;VAB5@8 2 :0@B>==V9 C?0:>2FV.

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

8@>1=8:.

« 0=10:AV 01>@0B>@V7 V

VAF57=0E>465==O.

=40AB@V0; @50 3, 520A 455001, =4VO.