

!" #&/

4;O <548G=>3> 70AB>AC20==O ?@5?0@0BC
(DICLOCAIN)

!;:04:
4VNGV @5G>28=8: diclofenac, lidocain5;
1 <; @>7G8=C 48:;>D5=0:C =0B@VN 37,5 <3; ;V4>:0W=C 3V4@>E;>@84C10 <3;
4>?>28=8: 2>40 4;O V=T:FV9, ?@>?V;5=3;V:>;L, 5B0=>; 96 %, =0B@VN <5B01VAC;LDVB(223),
48=0B@VN 545B0B, 0,1 @>7G8= =0B@VN 3V4@>:A84C.

V:0@AL:0 D>@<0. >7G8= 4;O V=T:FV9.

\$0@<0:>B5@0?52B8G=0 3@C?0. 5AB5@>W4=V ?@>B870?0;L=V V ?@>B8@52<0B8G=V 70A>18.
>4 " ! 0155.

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

>:070==O. @5?0@0B ?@87=0G0B8 ?@8 =0ABC?=8E AB0=0E:

- 703>AB@5==O 70?0;L=8E G8 4535=5@0B82=8E D>@< @52<0B87
- 3>AB@V =0?048 ?>403@8;
- =8@:>20 V ?5GV=:>20 :>;V:8;
- 1V;L, 70?0;5==O B0 =01@O: ?VA;O B@0< V EV@C@3VG=8E 2B@CG0=L.

@>B8?>:070==O.

- V428I5=0 GCB;82VABL 4> :>5=BV2 ?@5?0@0BC/00=5AB57CNG8E 70A>1V2, AC4<=>V =0?048 2
0=0<=57V, A?@8G8=5=V 70AB>AC20==O< ;V4>:0W=C.
- 002=VABL 2 0=0<=57V 5?V7>4V2 1@>=E>A?07AB@>3> @8=VBC, =070;L=8E ?>;V?V2,
:@>?82O=: 8 01> V=H8E 0;5@3VG=8E 70E2>@N20=L, 7C<>2;5=8E ?@89><<< 0F5B8;A0;VF8;>2>W
:8A;>B8 G8 V=H8E =5AB5@>W4=8E ?@>B870?0;L=8E ?@5?0@0BV2 ().
- 8@07:0 H;C=:0 V/01> 420=04FOB8?0;>W :8H:8 C AB04VW 703>AB@5==O, H;C=:>2>-.8H:>20
:@>2>B5G0 01> ?5@D>@0FVO.
- 0?0;L=V 70E2>@N20==O :8H5G=8:C (B0:V O: E2>@>10 @>=0 01> 28@07:>289 :>;VB).
- "O6:0 ?5GV=:>20 =54>AB0B=VABL (:;0A ! 70 H:0;>N '09;4-N, F8@>7 01> 0AF8B).
- !5@54=L>BO6:0 V BO6:0 =8@:>20 =54>AB0B=VABL (:;V@5=A :@50B8=V=C <30<;/E2), 3V?>2>;5
3V?>3V4@VO.
- "O6:0 A5@F520 =54>AB0B=VABL (:;0AIII-IV), 0B@V>25=B@8:C;O@=0 1;>:040 V ABC?5=O,
A8=4@<< A;01:>ABV A8=CA>2>3> 2C7;0, A8=4@< 40:A0, BO6:0 0@B5@V0;L=0 3V?>B5=7VO,
1@048:0@4VO, :0@4V>35==89 H>:.
- V:C20==O ?VA;O>?5@0FV9=>3> 1>;L>2>3> A8=4@>@>=0@=>3> HC=BC20==O (01> ?VA;O
70AB>AC20==O 0?0@0BC HBCG=>3> :@>2>>1V3C).
- 0FVT=B8 7 28A>:8< @878:<< ?VA;O>?5@0FV9=>W :@>2>B5GV, ?>@CH5=L 73>@B0==O :@>2V,
=5?>2=>3> 35<>AB07C, ?>@CH5=L 35<>?>57C 01> F5@51@>20A:C;O@=8E :@>2>B5G.
- V0AB5=VO.
- >@DV@VO.

!/?>AV1 70AB>AC20==O V 4>78. @5?0@0B 70AB>A>2C20B8 C 283;04V 2=CB@VH=L<<07>28E
V=T:FV9. >7C ?V418@0B8 V=482V4C0;L=>. V=V<0;L=C 5D5:B82=C 4>7C ?@87=0G0B8 ?@>BO3<< O:
<>30 :>@>BH>3> ?@>AC20==O< ?@5?0@0BC >1>2O7:>25 ?@>2545==O H:V@=>W ?@>18 =0
?V428I5=C GCB;82VABL 4> ;V4>:0W=C 3V4@>E;>@84C.
28G09=>N @07>2>N 4>7>N ?@5?0@0BC T 1 01B> 75 <3 48:;>D5=0:C =0B@VN), O:0 22>48BLAO
2=CB@VH=L<<07>2> 1 @07 =0 4>1C H;OE<< 3;81:>:>W V=T:FVW C 25@E=V9 7>2=VH=V9 :204@0=B
AV4=8G=>3> <070. >7G8= A;V4 28:>@8AB0B8 >4@07C ?VA;O 2V4:@8BBO 0@8AB0=>3> @>7G8=C
?>B@V1=> CB8;V7C20B8.

@8 A8;L=8E 1>;OE (=0?@8:;04 ?@8 :>;V:0E) ?@5?0@0B <>6=0 22>48B8 2 @078 =0 4>1C 7 V=B5@20;>< C :V;L:0 3>48=, >1>2O7:>2> 7

"@820;VABL ?0@5=B5@0;L=>3> 70AB>AC20==O ?@5?0@0BC =5<0T ?5@528IC20B8 2 4=V2. 5 70AB>A>2C20B8 ?@5?0@0B 4;O 2=CB@VH=L>25==>W V=T:FVW/V=DC7VW.

>IVG=V @50:FVW. >IVG=V @50:FVW ;:0A8DV:>20=V 70 G0AB>B>N 28=8:=5==O: 4C65 G0AB> (>=1/10), G0AB> (>=1/100, <1/10), =5G0AB> (>=1/1000, <1/100), @V4:> (>=1/10000, <1/1000), 4C65 @V4:> (<1/10000).

I>:C :@>2V V ;VW A8AB5<8: 4C65 @V4:> B@><1>F8B>?5=VO, ;59:>?5=VO, 0=5

I>:C VW A8AB5<8: @V4:> @50:FVW 3V?5@GCB;82>ABV (0=0DV;0:B8G=V V ?A524>0=0DV;0:B8G=V @50:FVW, C B. G. 0@B5@V0;L=0 3V?>B5=7VO V H>:); 4C65 @V4:> 0=3V>=52@>B8G=89 =01@O: (C B. G. =01@O: >1;8GGO), 2V4GCBBO 60@C, E>;>4C 01> >=V:.

I>:C =5@2>2>W A8AB5<8: G0AB> 3>;>2=89 1V;L, 70?0<>@>G5==O; @V4:> A>;82VABL; 4C65 @V4:> ?0@5AB57VW, ?>@CH5==O ?0<OBV, AC4<8, 70=5?>:>T==O, B@82>6=VABL, 71C465==O, =5@2>7=VABL, B@5<>@, B8:, B@87<, @CE>289 =5A?>:V9, 59D>@VO, 0A5?B8G=89 <5=V=3VB, ?>@CH5==O A<0:C, V=AC;LB, ?>@CH5==O GCB;82>ABV/2V4GCBBO 4>B8:C, ?0@0;VG, A?;CB0=VABL/2B@0B0 A2V4<>ABV, A;01:VABL, 457>@VT=B0FVO, 45?@5AVO, 157A>==O, =VG=V :>H<0@8, 4@0BV2;82VABL, ?A8EVG=V @>7;048.

I>:C >@30=V2 GCBBO: G0AB> 25@B83>; 4C65 @V4:> ?>@CH5==O, 70BC<0=5==O, =5GVB:VABL 7>@C, 48?;>?VO, =VAB03<, <83BV==O «:» ?5@54 >G8<0, @>7H8@5==O 7V=8FL, A2VB;>1>07=L, >1>@>B=0 A;V?>B0, :=N=:B82VB, 73> :>;L>@C, B>:A8G=0 0<1;V>?VO, ?>@CH5==O A;CEC, HC< C 2CE0E, 3V?5@0:C7VO.

I>:C A5@F52>-AC48==>W A8AB5<8: 4C65 @V4:> ?>A8;5=5 A5@F518BBO, B0EV:0@4VO, 1V;L C 3@C4=V9 ;:VBFV, V=D0@:B, C?>2V;L=5==O ?@>2V4=>ABV A5@FO, ?>?5@5G=0 1;>:040 A5@FO, DV1@8;OFVO H;C=>G:V2, 7C?8=:0 A5@F52>W 4VO;L=>ABV, ?5@8D5@8G=0 207>48;0B0FVO, :>;0?A, A5@F520 =54>AB0B=VABL, 0@B5@V0;L=0 3V?5@B5=7VO/3V?>B5=7VO, 20A:C;VB, 0@8B

I>:C >@30=V2 48E0==O: @V4:> 0AB<0 (C B. G. 7048H:0), @8=VB, 1@>=E>A?07<; 4C65 @V4:> ?=52 <>=VB, ?@83=VG5==O/7C?8=:0 48E0==O, CB@C4=5=5 48E0==O, ?0@0;VG 48E0;L=8E <□O7V2.

I>:C B@02=>W A8AB5<8: G0AB> 014>B0, 1;N20==O, 4V0@50, 014> 30AB@8B, H;C=:>2>:8H:>2V :@>2>B5GV, 1;N20==O 7 4>

I>:C H:V@8: G0AB> 28A8?0==O; @V4:> :@>?820=:0, 3V?5@B5@B5@B>284V;5==O, 1;V4VABL H:V@8; 4C65 @V4:> 1C;L>7=5 28A8?0==O, 5:75<0, 5@8B5<0, @<=0 5@8B5<0, A8=4@< !BV25=A0-6>=A>=0, A8=4@< 09T;:0, 5:AD>;V0B82=89 45@<0B8B, 0;>?5FVO, D>B>GCB;82VABL, ?C@?C@0, 0;5@3VG=0 ?C@?C@0, A25@1V6.

I>:C A5G>284V;L=>W A8AB5<8: G0AB> 70B@8@30=V7 <8<>2V;L=5 A5G>28?CA:0==O, 7=865==O ;V1V4> V/G8 ?>B5=FVW, 3>AB@0 =8@:>20 =54>AB0B=VABL, 35<0BC@VO, ?@>B5W=C@VO, V=B5@AB8FV0;L=89 =5D@>8B, =5D@>B8G=89 A8=4@<, =8@:>289 ?0?V;O@=89 =5:@>7.

50:FVW C G0AB> 1V;L, 3V?5@53> ?5GV==O 01> CIV;L=5==O B:0=8=; @V4:> =01@O:, 70B25@4V==O, =5:@>7; 4C65 @V4:> 01AF5A.

A=CNBL 40=V ?@> <>6;82VABL ?V428I5==O @878:C 28=8:=5==O 0@B5@V0;L=>W B@<1>5<1>;VW (=0?@8:;04 V=D0@:B :0@40 01> V=AC;LB) ?@8 B@820;>AC20==V 48:;>D5=0:C C 28A>:8E 4>70E (?>=04 150 <3 =0 4>1C).

5@54>7C20==O. "8?>2V ;:V=VG=V A8<8 ?5@54>7C20==O 48:;>D5=0:C =0B@VN =52V4>7C20==O <>6CBL 28=8:=CB8 1;N20==O, H;C=:>2>:8H:>2V :@>2>B5GV, 4V0@50, 70?0<>@>G5==O, HC< C 2CE0E 01> AC4<8. # 28?04:C B06:>3> >B@CT==O <>6;82V 3>AB@0 =8@:>20 =54>AB0B=VABL V C@065==O ?5GV=:8.

5@H8<8 A8<0<8 ?5@54>7C20==O ;V4>:0W=C 3V4@>E;>@84C <>6CBL 1CB8 >=V

V:C20==O: ?V4B@848 V A8<0B8G=5 ;V:C20==O 4;O CAC=5==O B0:8E CA:;04=5=L O: 0@B5@V0;L=0 3V?>B5=7VO, =8@:>20 =54>AB0B=VABL, AC4<8, ?>4@07=5==O A;87>2>W >1>;>=:8 B@02=>3> B@0:BC V ?@83=VG5==O 48E0==O. !?5F8DVG=0 B5@0?VO, =0?@8:;04 D>@A>20=89 4VC@57, 4V0;V7 01> 35<>?5@DC7VO, =5 <0T >A>1;82>3> 7=0G5==O ?@8 282545==V, 2@0E>2CNG8 28A>:89 ABC?V=L 72O7C20==O F8E ?@5?0@0BV2 7 1V;:0<8 ?;07<8 B0 5:AB5=A82=89 <5B01>;V7

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N. @5?0@0B ?@>B8?:>:070=89 C
?5@V>4 203VB=>ABV. @8 =5>1EV4=>ABV 70AB>AC20==O ?@5?0@0BC 3>4C20==O 3@C44N A;V4
?@8?8=8B8.

0AB>AC20==O 48;:>D5=0:C <>65 ?>@CH8B8 @5?@>4C:B82=C DC=:FVN 6V=:8, B><5=4>20=89 6V=:0
<, O:V ?>=CNBL 203VB=VABL. V=:0, C O:8E T ?@>1;5<8 V7 70G0BBO< 01> O:V ?@>E>48;8
>1AB565==O I>4> 157?;V44O, 4>FV;L=> ?5@53;O=CB8 2V4D5=0:C.

VB8. 5 70AB>A>2C20B8 4VBO

A>1;82>ABV 70AB>AC20==O. @8 ;V:C20==V <>6CBL 28=8:0B8 28@07:8, :@>2>B5GV 01>
?5@D>@0FVW B@02=>3> B@0:BC 7 01> 157 ?>?5@546C20;L=8E A8 A5@9>7=8E H;C=:>2>-.8H:>28E
O28I 2 0=0<=57V.

@8 B0:8E 70E2>@N20==OE O: ;V=VG=> ?V4B25@465=0 VH5@>10 A5@FO, F5@51@>20A:C;O@=0
?0B>;>3VO, >1;VB5@CNG89 0B5@>A;:5@>7 ?5@8D5@8G=8E 0@B5@V9 01> ?0FVT=B0< V7 3@C?8
@878:C (=0?@8:;04 ?@8 =0O2=>ABV 0@B5@V0;L=>W 3V?5@B5=7VW, 3V?5@;V?V452>3> 4V015BC,
?@8 ?0;V==V), 48;:>D5=0: A;V4 70AB>A>2C20B8 BV;L:8 ?VA;O @5B5;L=>3> 0=0;V7C<>6;828E
@878:V2 V ?5@5203 B0:>3> ;V:C20==O.

2545==O ;V4>:0W=C <>6CBL 74V9A=N20B8 BV;L:8 <548G=V ?@0FV2=8:8.

!;V4 7 >15@56=VABN ?@87=0G0B8 ?@5?0@0B8, I>:0W=, ?0FVT=B0< ;VB=L>3> 2V:C, E2>@8<=0
5?V;5?AVN, ?@8 ?>@CH5==V ?@>2V4=>ABV A5@FO, ?@8 48E0;L=V9 =54>AB0B=>ABV. "0:>6 7
>15@56=VABN V C <5=H8E 4>70E 70AB>A>2C20B8 ?0FVT=B0< V7 A5@F52>N =54>AB0B=VABN ?>3>
ABC?5=O, 0@B5@V0;L=>N 3V?>B5=7VTN ?>3> ABC?5=O, =5?>2=>N AV-1;:>:04>N, ?>@CH5==O<8
DC=:FVW ?5GV=:8 ?>3> ABC?5=O, ?VA;O >?5@0FV9 =0 A5@FV, ?@8 35=5B8G=V9 AE8;L=>ABV 4>
7;>O:VA=>W 3V?5@B5@A;01;5=8< E2>@8

V4 G0A 70AB>AC20==O ;V4>:0W=C >1>2O7:>28< T :=B@>;L . # 28?04:C ?>@CH5=L 4VO;L=>ABV
A8=CA>2>3> 2C7;0, ?>4>265==O V=B5@20;C P-Q, @>7H8@5==O QRS 01> ?@8 @>728B:C 0@8B
AC20==O< ?@8 70E2>@N20==OE A5@FO =5>1EV4=> =>@<0;V7C20B8 @V25=L :0;VN C :@>2V.
A:V;L:8 ;V4>:0W= G8=8BL 28@065=C 0=B80@8B15@56=VABN 70AB>A>2C20B8 ?@5?0@0B >A>10<
7V A:0@30<8 =0 0@8B

@8 2=CB@VH=L<<□O7>2>:0W=C <>65 ?V428I8B8AO :=F5=B@0FVO :@50B8=V=C, I> <>65
?@8725AB8 4> ?><8;:8 ?@8 ?>AB0=>2FV 4V03=>7C 3>AB@>3> V=D0@:BC :0@40.

!;V4 C=8:0B8 70AB>AC20==O ?@5?0@0BC 7 A8AB5<=8<8 , 2;:NG0NG8 A5;5:B82=V V=3V1VB>@8
F8;:>:A835=078-2, G5@57 2V4ACB=VABL 1C4L-O:>W A8=5@3VG=>W :=@8ABV V<>6;82>ABV
@>728B:C 4>40B:>28E ?>1VG=8E 5D5:BV2.

C65 @V4:> C 72O7:C 7 70AB>AC20==O< <>6CBL A?>AB5@V30B8AO A5@9>7=V @50:FVW 7 1>:C
H:V@8, 2;:NG0NG8 5:AD>;V0B82=89 45@<0B8B, A8=4@<< !BV25=A0-6=>A=>0 V A8=4@<< 09T;:0.
0928I89 @878: 28=8:=5==O 40=8E @50:FV9 C ?0FVT=V2 VA=CT =0 ?>G0B:C :C@AC ;V:C20==O, C
1V;LH>ABV 28?04:V2 ?>O20 F8E @50:FV9 2V41C20TBLAO C <560E ?5@H>3> 7=0:0E ?>O28 28A8?0=L
=0 H:V@V, C@065==OE A;87>28E >1>;>=: 01> 1C4L-O:8E V=H8E >7=0: 3V?5@GCB;82>ABV
?@5?0@0B =5>1EV4=> 2V4

>6CBL B0:>6 28=8:=CB8 0;5@3VG=V @50:FVW, C B. G. 0=0DV;0:B8G=V/0=0DV;0:B>W4=V. 0B@VN
<5B01VAC;LDVB C @>7G8=V 4;O V=T:FV9<>65 ?@8725AB8 4> >:@5<8E BO6:8E @50:FV9
3V?5@GCB;82>ABV V 1@>=E>A?07

7024O:8 A2>W< D0@<0:>48=0

?;82 =0 B@02=C A8AB5

8;:>D5=0: =5>1EV4=> 70AB>A>2C20B8 ?V4 <548G=8< =03;O4<< V 7 >15@56=VABN ?0FVT=B0< V7 A8
<0<8, I> 2:07CNBL =0 H;C=:>2>-.8H:>2V 70E2>@N20==O, 01> 7 0=0<=57<<, I> A2V4G8BL ?@>
=0O2=VABL 28@07:8 H;C=:0 01> :8H5G=8:C, :@>2>B5GV 01> ?5@D>@0FVW B@02=>3> B@0:BC. 878:
H;C=:>2>-.8H:>28E :@>2>B5G 28I89 ?@8 ?V428I5==V 4>7 C ?0FVT=V2 7 28@07:>N 2 0=0<=57V,
>A>1;82> CA:;04=5=>N :@>2>B5G5N 01> ?5@D>@0FVTN, 0 B0:>6 2 >AV1 ;VB=L>3> 2V:C. ">

)>1 7<5=H8B8 @878: B@02=8E ?>@CH5=L C ?0FVT=V2 7 28@07:>N 2 0=0<=57V, >A>1;82>
CA:;04=5=>N :@>2>B5G5N 01> ?5@D>@0FVTN, 0 B0:>6 2 >AV1 ;VB=L>3> 2V:C, ?0FVT=V2 7V A;01:8
< 74>@>2O< 01> 7 <0;>N <0A>N BV;0, ?0FVT=V2, O:V @53C;O@=> ?@89<0NBL =87L:V 4>78
0F5B8;A0;VF8;>2>W :8A;>B8 01> V=HV ;V:0@AL:V 70A>18, I> ?V428ICNBL @878: =51060=>W 4VW
=0 B@02=89 B@0:B, 4>FV;L=> ?@87=0G0B8 ?@5?0@0B C :<1V=0FVW 7 70A>10<8, O:V <0NBL

70E8A=C 4VN =0 A;87>2C >1>;>=:C H;C=:0 (=0?@8::;04 7 V=3V1VB>@0<8 ?@>B>==>W ?> ?@>AB>;>
<). ;O B0:8E ?0FVT=BV2 @5:><5=4CTBLAO ?>G8=0B8 V ?V4B@8
0AB5@565==O B0:>6 ?>B@V1=V 4;O E2>@8E, O:V >B@818, I> <>6CBL ?V428I8B8 @878: 28@07:8 01>
:@>2>B5GV, B0:V O: A8AB5<=V :>@B8:>AB5@>W48, 0=B8:>03C;O=B8, 0=B8B@><1>B8G=V 70A>18
01> A5;5:B82=V V=3V1VB>@8 72>@>B=>3> 70E>;5==O A5@>B>=V=C (!!).
@5?0@0B =5>1EV4=> 7 >15@56=VABN ?@87=0G0B8 E2>@8<, 2 0=0<=57V O:8E T 70?0;L=V
70E2>@N20==O :8H5G=8:C, B0:V O: E2>@>10 @>=0 01> =5A?5F8DVG=V 28@07:>2V :>;VB8, B0
2AB0=>2;N20B8 @5B5;L=89 <548G=89 =03;O4 V 2V4?>2V4=V 70AB5@56=V 70E>48 C 72O7:C 7 B8<, I>
WE AB0= <>65 703>AB@N20B8AO.
;O ?0FVT=BV2 ;VB=L>3> 2V:C ;V:C20==O <>65 <0B8 1V;LH A5@9>7=V =0A;V4:8. ">28==V ?>2V4>
<;OB8 A2>T 1C4L-O:V =5728G=V A8<8 7 1>:C B@02=>W A8AB5<8. /:I> ?@8 70AB>AC20==V
?@5?0@0BC C ?0FVT=BV2 @>72820TBLAO H;C=:>2>-.8H:>20 :@>2>B5G0 01> 28@07:0 B@02=>3>
B@0:BC, ?@5?0@0B =5>1EV4=> 2V4
A>1;82>ABV 70AB>AC20==O E2>@8< =0 1@>=EV0;L=C 0AB
?0FVT=BV2 7 1@>=EV0;L=>N 0AB<>N, A57>==8<8 0;5@3VG=8<8 @8=VB0<8, E@>=VG=8<
>1AB@C:B82=8< 70E2>@N20==O <;535=L 01> E@>=VG=8<8 V=D5:FVO<8 @5A?V@0B>@=>3>
B@0:BC (>A>1;82> O:I> 2>=8 0A>FV9>20=V 7 A8<0<8, I> =0304CNBL A8<0B8:C 0;5@3VG=>3>
@8=VBC) G0ABVH5, =V6 2 V=H8E ?0FVT=BV2, 7CAB@VG0NBLAO B0:V @50:FVW =0 ?@89< O:
703>AB@5==O 0AB<8 (B0: 720=0 =5?5@5=>A8B@VT=>20 0AB<0, 0A?V@8=>20 0AB<0). &5 B0:>6
AB>ACTBLAO ?0FVT=BV2 7 0;5@3VTN 4> V=H8E @5G>28=, =0?@8::;04 C 283;O4V H:V@=>3>
28A8?0==O, A25@156C 01> :@>?82O=:8.
A>1;82C >15@56=VABL =5>1EV4=> ?@>O2;OB8 ?@8 70AB>AC20==V 48:;>D5=0:C ?0FVT=B0<, E2>@8
<=0 1@>=EV0;L=C 0ABA:V;L:8 ?@8 FL>
?;82 =0 35<0B>;>3VG=V ?>:07=8:8
A:V;L:8 <>6CBL B82> ?@83=VGC20B8 03@530FVN B@><1>F8BV2, ?@8 B@820;>D5=0:C, O: V V=H8E
, @5:><5=4CTBLAO :>=B@>;N20B8 35<0B>;>3VG=V ?>:07=8:8. V:C20==O ?0FVT=BV2 7 ?>@CH5==O
<8 35<>AB07C =5>1EV4=> ?@>2>48B8 ?V4 =03;O4<< ;V:0@O.
A>1;82>ABV 70AB>AC20==O E2>@8< 7 ?>@CH5=>N DC=:FVTN ?5GV=:8
%2>@8< 7 ?>@CH5=>N DC=:FVTN ?5GV=:8 ?@8 ?@87=0G5==V 48:;>D5=0:C =5>1EV4=89 @5B5;L=89
<548G=89 =03;O4, >A:V;L:8 ?@8 ?@89>
0 B;V ;V:C20==O <>65 ?V428IC20B8AO @V25=L >4=>3> 01> :V;L:>E ?5GV=:>28E D5@<5=BV2 :@>2V.
"0:V 7 AC?@>2>46CNBLAO ;;V=VG=8<8 A8<0<8. # 1V;LH>ABV B0:8E 28?04:V2 7@>AB0==O F8E
?>:07=8:V2 70;8H0TBLAO C <560E 3@0=8G=8E 7=0G5=L. '0AB> (C 2,5 % 28?04:V2) 2V47=0G0;>AO ?>
AB0==O F8E ?>:07=8:V2 28I5 =>@<8 (2V4 ≥ 3 4> < 8 × 25@E=O <560 =>@<8), B>4V O: G0AB>B0
7=0G=>3> 7@>AB0==O @V2=V2 F8E D5@<5=BV2 (≥ 8 × 25@E=O <560 =>@<8) AB0=>28;0 ?@81;87=>
1 %. # 0,5 % ?0FVT=BV2, >:@V< ?V428I5==O @V2=V2 ?5GV=:>28E D5@<5=BV2, @>728=C;8AO
;;V=VG=> <0=VD5AB=V C@065==O ?5GV=:8. VA;O 2V4:07=8:V2 70728G09 ?>25@B0TBLAO 4> =>@<8.
/:I> ?@8 ?@89> ?>3V@HCNBLAO, O:I> 28=8:0NBL ;;V=VG=V >7=0:8 01> A8<8 70E2>@N20=L ?5GV=:8
(=0?@8::;04 35?0B8B) 01> V=HV ?@>O28 (=0?@8::;04 5>78=>DV;VO, 28A8?0==O), 48:;>D5=0: ?>B@V1=>
2V4

A>1;82>ABV 70AB>AC20==O E2>@8< V7 ?>@CH5==O<8 DC=:FVW A5@FO V =8@>:
@>AB03;0=48=8 2V4V3@0NBL 206;82C @>;L C ?V4B@8<0==V =8@:>2>3> :@>2>>1V3C, B>:8<8 4>70
<8 G0AB> (C 1-10 % 28?04:V2) 7C<>2;NT @>728B>: =01@O:V2 V 0@B5@V0;L=>W 3V?5@B5=7VW.
A:V;L:8 ?@8 ;V:C20==V ?>2V4<;O;>AO ?@> 70B@8A>1;82>W >15@56=>ABV A;V4 4>B@8<0T O2=89
2?;82 =0 DC=:FVN =8@>;; ?0FVT=B0< V7 ACBBT28< 7=865==O< ?>70;;VB8==>3> >1TW ?@8G8=8,
=0?@8::;04 C ?5@54- 01> ?VA;O>?5@0FV9=>4V ?@8 A5@9>7=8E EV@C@3VG=8E 2B@CG0==OE. /:I>
B0:V ?0FVT=B8 ?@89<0NBL 48:;>D5=0:, C O:>ABV 70AB5@56=>3> 70E>4C @5:><5=4CTBLAO
:>=B@>;N20B8 AB0= DC=:FVW =8@>:. VA;O 2V4

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. 0FVT=B0< 7 ?>@CH5==O< 7>@C, 70?0<>@>G5==O<, 25@B83>, A>=;82VABN
01> V=H8<8 ?>@CH5==O<8 7 1>:C =5@2>2>W A8AB5<8 =5>1EV4=> CB@8<>1V;5< 01> @>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. @8 >4=>G0A=>AC20==V
48:;>D5=0: <>65 71V;LHC20B8 :=F5=B@0FVW ;VBN V 483>:A8=C C ?;072V, B<5=4CTBLAO
:=B@>;N20B8 WE @V2=V C A8@>20BFV :@>2V.

/: V V=H8E , 70AB>AC20==O 48:;>D5=0:C >4=>G0A=> 7 4VC@5B8:0<8 01> 0=B83V?5@B5=782=8<8
?@5?0@0B0<8 (=0?@8:;04 β-1;>;0B>@0<8, V=3V1VB>@0<8 \$) <>65 7C<>2;N20B8 7=865==O
0=B83V?5@B5=782=>3> 5D5:BC F8E ?@5?0@0BV2. "0:V :<1V=0FVW A;V4 70AB>A>2C20B8 7
>15@56=VABN, 0@B5@V0;L=89 B8A: C F8E ?0FVT=BV2, >A>1;82> ;VB=L>3> 2V:C, A;V4
?5@V>48G=> :=B@>;N20B8. 0FVT=B0< =5>1EV4=> 26820B8 =0;56=C :V;L:VABL @V48=8 V @5:>
<5=4CTBLAO 74V9A=N20B8 :=B@>;L =8@:>2>W DC=:FVW =0 ?>G0B:C AC?CB=L>W B5@0?VW V
?5@V>48G=> C ?>40;LH>A>1;82> C 28?04:C ?@89>@V2 \$, 2@0E>2CNG8 7@>AB0NG89 @878:
=5D@>B>:A8G=>ABV.

F5B07>;02V 4VC@5B8:8 7<5=HCNBL 5D5:B ;V4>:0W=C C @57C;LB0BV AB2>@5==O 3V?>:0;VT
4=>G0A=5 70AB>AC20==O ?@5?0@0BC 7 :0;V9715@V30NG8<8 4VC@5B8:0<8 <>65 ?@872>48B8 4>
3V?5@:0;VT1EV4=5 ?5@V>48G=5 287=0G5==O @V2=V2 :0;VN C A8@>20BFV :@>2V.

0AB>AC20==O 48:;>D5=0:C >4=>G0A=> 7 @V7=8<8 A8AB5<=8<8 01> 3;N:>:=@B8:>AB5@>W40<8
<>65 A?@8OB8 @>728B:C =51060=8E ?>1VG=8E 5D5:BV2 7 1>:C B@02=>W A8AB5<8.

5:>5=4CTBLAO 7 >15@56=VABN 70AB>A>2C20B8 48:;>D5=0: 7 0=B8:>03C;O=B0<8 B0 0=B8B@>
<1>F8B0@=8<8 ?@5?0@0B0<8, B> WE :<1V=>20=5 70AB>AC20==O <>65 ?V428I8B8 @878:
:@>2>B5GV. >:07V2 2?;82C 48:;>D5=0:C =0 4VN 0=B8:>03C;O=BV2 =5 28O2;5=>, 0;5 T >:@52V4>
<;5==O ?@> ?V428I5==O @878:C 35<>@03VG=8E CA:;04=5=L C ?0FVT=BV2, O:V 70AB>A>2C20;8
>4=>G0A=> 48:;>D5=0: V 0=B8:>03C;O=B8. # 7207:C 7 F8< @5:>5=4CTBLAO @5B5;L=89 =03;04 70
B0:8<8 ?0FVT=B0<8.

4=>G0A=5 70AB>AC20==O A8AB5<=8E V !! <>65 71V;LHC20B8 @878: H;C=:>2>:-:8H:>28E :@>2>B5G.
AB0=>2;5=>, I> 48:;>D5=0: <>6=0 ?@87=0G0B8 @07>< V7 ?5@>@0;L=8<8 3V?>3;V:5:@52V4><;5==O
?@> 3V?>3;V:5D5=0:C, O:V ?>B@51C20;8 77 3V?>3;V:5
5:>5=4CTBLAO 7 >15@56=VABN ?@87=0G0B8 ?@>BO3< 24 3>48= 4> 01> ?VA;O 70AB>AC20==O
<5B>B@5:A0BC, >A:V;L:8 :=F5=B@0FVO <5B>B@5:A0BC C :@>2V V 9>3> B>:A8G=VABL<>6CBL
7@>AB0B8.

8:;>D5=0:, O: V V=HV , <>65 71V;LHC20B8 =5D@>B>:A8G=VABL F8:;>A?>@8=C G8 B0:@>;VT
AB03;0=48=8 =8@>:. # 7207:C 7 F8< ?@5?0@0B A;V4 ?@87=0G0B8 C <5=H8E 4>70E, =V6 ?0FVT=B0<,
O:V =5 >B@8A?>@8= G8 B0:@>;V

A=CNBL >:@52V4><;5==O ?@> @>728B>: AC4<, O:V, <>6;82>, 1C;8 @57C;LB0B>< >4=>G0A=>3>
70AB>AC20==O EV=>;>=V2 V .

4=>G0A=5 70AB>AC20==O 48:;>D5=0:C V :>;5AB8?>;C 01> E>;5AB8@0
@5?0@0B8, O:V AB8*Hypericum perforatum*) B>I>, B5>@5B8G=> 740B=V 7<5=HC20B8 :=F5=B@0FVW
48:;>D5=0:C C ?;07

V407>;0<, β-1;>;0B>@8 (?@>?@0=>;>; B>I>), F8<5B848=, ?5?B848=, 1C?V20:0W=, EV=V48=, 487>?V@0
:0W=C C A8@>20BFV :@>2V, 7<5=HCNG8 9>3> ?5GV=:>289 <5B01>;V7<, ?>A8;NNG8 5D5:B8 (C B. G.
B>:A8G=V) V ?V428ICNG8 @878: @>728B:C 1@048:0@4VW V 0@B5@V0;L=>W 3V?>B5=7VW. ">
AC20==V B0:8E :=<1V=0FV9 4>7C ;V4>:0W=C =5>1EV4=> 7<5=HC20B8.

V4>:0W= ?>A8;NT 0=0;357CNG89 5D5:B =0@>B8G=8E 0=0;L35B8:V2 (<>@DV= B>I>), ?@83=VG5==O
48E0==O.

@8 V=B>:A8:0FVW A5@F528<8 3;V:>7840<8 (3;V:>7840<8 =0?5@ABO=:8 B>I>);V4>:0W= <>65
?>A8;N20B8 BO6:VABL AV-1;>;048. V4>:0W= ?>A;01;NT :0@4V>B>=VG=89 5D5:B A5@F528E
3;V:>784V2.

4=>G0A=5 70AB>AC20==O 48:;>D5=0:C V :>;5AB8?>;C 01> E>;5AB8@0
@5?0@0B8, O:V AB8*Hypericum perforatum*) B>I>, B5>@5B8G=> 740B=V 7<5=HC20B8 :=F5=B@0FVW
48:;>D5=0:C C ?;07

V407>;0<, β-1;>;0B>@8 (?@>?@0=>;>; B>I>), F8<5B848=, ?5?B848=, 1C?V20:0W=, EV=V48=, 487>?V@0
:0W=C C A8@>20BFV :@>2V, 7<5=HCNG8 9>3> ?5GV=:>289 <5B01>;V7<, ?>A8;NNG8 5D5:B8 (C B. G.
B>:A8G=V) V ?V428ICNG8 @878: @>728B:C 1@048:0@4VW V 0@B5@V0;L=>W 3V?>B5=7VW. ">
AC20==V B0:8E :=<1V=0FV9 4>7C ;V4>:0W=C =5>1EV4=> 7<5=HC20B8.

V4>:0W= ?>A8;NT 0=0;357CNG89 5D5:B =0@>B8G=8E 0=0;L35B8:V2 (<>@DV= B>I>), ?@83=VG5==O
48E0==O.

@8 >4=>G0A=>AC20==V 7 0=B80@8B40@>=><, 25@0?0<, EV=V48=>< B>I>), 10@1VBC@0B0<8 (D5=>10@1VB0;><) G8 ?@>B8AC4><=8<8 70A>10<8 (?>EV4=8<8 3V40=B>W=C) <>6;825 ?@8A:>@5==O <5B01>;V7:0W=C C ?5GV=FV, 7=865==O :=F5=B@0FVW C :@>2V, ?>A8;5==O :0@4V>45?@5A82=>W 4VW.

@8 >4=>G0A=>AC20==V 7 A540B82=8<8 V A=>4V9=8<8 70A>10<8 <>6;825 ?>A8;5==O ?@83=VGC20;L=>W 4VW =0 F5=B@0;L=C =5@2>2C A8AB5< ?V428ICTBLAO @878: @>728B:C H;C=>G:>2>W 0@8B

\$5=VB>W= ?>A8;NT :0@4V>45?@5A82=C 4VN ;V4>:0W=C.

V4>:0W= ?>A8;NT ?@83=VGC20;L=C 4VN =0 48E0;L=89 F5=B@ 70A>1V2 4;O =0@:>7C (35:A>10@1VB0;, BV>?5=B0; =0B@VN 2=CB@VH=L>25==>), @5;0:A0FVN :C@0@5?>4V1=8E ?@5?0@0BV2 (<>6;8289 ?0@0;VG 48E0;L=8E <□O7V2).

@8 70AB>AC20==V 7 ?>;V< =5>1EV4=89 :=B@>;L DC=:FVW 48E0==O.

V4>:0W= <>65 7=86C20B8 :=F5=B@0FVN @8D02V.

@8 >4=>G0A=>AC20==V 7 =>2>:0W=><, =>2>:0W=0<, ?@>:0W=0< <>6;825 71C465==O &!, <0@5==O, 30;NF8=0FVW; 7 ?@>?0D5=>=>< <>6;825 71V;LH5==O B@820;>ABV V ?V428I5==O BO6:>ABV ?>1VG=8E 5D5:BV2 7 1>:C &!

=3V1VB>@8 (DC@07>;V4>=, ?@>:0@1078=, A5;53V;V=) ?V428ICNBL @878: @>728B:C 0@B5@V0;L=>W 3V?>B5=7VW V ?@>;>=3CNBL 0=5AB57CNGC 4VN ;V4>:0W=C. # ?5@V>4 ;V:C20==O V=3V1VB>@0<8 =5 A;V4 70AB>A>2C20B8 ;V4>:0W= ?0@5=B5@0;L=>.

V4>:0W= <>65 ?>A8;N20B8 4VN ?@5?0@0BV2, I> 7C<>2;NNBL 1;>:04C =5@2>2><O7>2>W ?5@540GV, >A:V;L:8 >AB0==V 7<5=HCNBL ?@>2V4=VABL =5@2>28E V

B0=>; ?>A8;NT ?@83=VGC20;L=C 4VN ;V4>:0W=C =0 48E0==O.

704@8=, 3;N:03>= ?V428ICNBL ;V@5=A ;V4>:0W=C; =>@5?V=5D@8=, <5:A8;5B8= 7=86CNBL, ?5GV=:>289 :@>2>BV: B0:>6 7<5=HCTBLAO. 07>:=AB@8:B>@8 (5?V=5D@8=, <5B>:A02V;L=5==N 2A<>:BC20==O ;V4>:0W=C V ?@>;>=3CNBL 4VN >AB0==L>3>.

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

\$0@<0:>48=0 @5?0@0B D5=0:C =5AB5@>W4=C 4VNGC @5G>28=C 7 28@065=8<8 ?@>B8@52 <0B8G=8<8, ?@>B870?0;L=8<8, 7=51>;N20;L=8<8 B0 0=B8?V@5B8G=8<8 2;0AB82>ABO<8.

@83=VG5==O 1V>A8=B57C ?@>AB03;0=48=V2 22060TBLAO >A=>2=8< <5E0=V7<< 9>3> 4VW.

@>AB03;0=48=8 2V4V3@0NBL 7=0G=C @>;L C @>728B:C 70?0;5==O, 1>;N V ?V428I5==O B5 @8 @52<0B8G=8E 70E2>@N20==OE ?@>B870?0;L=V V 7=51>;N20;L=V 2;0AB82>ABV ?@5?0@0BC >1C<>2;NNBL ;V=VG=C 2V4?>2V4L, O:0 E0@0:B5@87CTBLAO 28@065=8< 7=8:=5==O< >7=0: V A8 :>N, 1V;L ?@8 @CE0E, @0=:>20 A:CBVABL V =01@O: AC3;>1V2, 0 B0:>6 ?>:@0I5==O

DC=:FV>=0;L=8E 2;0AB82>AB59 AC3;>1V2. @8 ?>ABB@02<0B8G=8E/?VA;O>?5@0FV9=8E 70?0;5==OE 48:;>D5=0: 7C<>2;NT H284:5 7<5=H5==O @0?B>2>3> 1>;N V 1>;N ?@8 @CE0E, 0 B0:>6 7 <5=HCT =01@O:8, A?@8G8=5=V 70?0;5==O< V @0=0<8.

@8 >4=>G0A=>AC20==V 4;O ;V:C20==O ?VA;O>?5@0FV9=>3> 1>;N 48:;>D5=0: 7=0G=> 7=86CT ?>B@51C 2 >?V>W40E. @5?0@0B <>65 ?>A8;8B8 28@065=89 7=51>;N20;L=89 2?;82 =0 ?>;V =5@52 <0B8G=>3> ?>E>465==O ?@>BO3>< 15-30 E28;8= ?VA;O 22545==O.

@5?0@0B >A>1;82> 5D5:B82=89 ?@8 70AB>AC20==V 4;O ?>G0B:>2>W B5@0?VW 70?0;L=8E V 4535=5@0B82=8E @52<0B8G=8E 70E2>@N20=L, 0 B0:>6 4;O ;V:C20==O 1>;N, 7C<>2;5=>3> =5@52 <0B8G=8< 70?0;5==O

\$0@<0:>:V=5B8:0. !5@54=V9 >1T< @>7?>4V;C 48:;>D5=0:C =0B@VN AB0=>28BL 0,12-0,17 /:3, 72O7C20==O 7 1V;:0<8 ?;07<8 :@>2V 2V41C20TBLAO 1V;LH =V6 =0 99 %.

"5@0?52B8G=0 :=F5=B@0FVO 48:;>D5=0:C C ?;072V AB0=>28BL 0,7-2

>2B>@=5 22545==O ?@5?0@0BC =5 7C<>2;NT 1C4L-O:8E 7:C =8@>:. @8 4>B@8<0==V @5:> <5=4>20=8E V=B5@20;V2 @30=V7

8:;>D5=0: ?@>=8:0T C A8=>2V0;L=C @V48=C, 45 9>3> !_{max} 287=0G0TBLAO G5@57 2-4 3>48=8 ?VA;O B>3>, O: 1C;8 >B@8<0=V 7=0G5==O ?V:>2>W :=F5=B@0FVW,T_{1/2} ?@8 FL>28BL 3-6 3>48=. "> 4-6 3>48= ?VA;O 22545==O ?@5?0@0BC :=F5=B@0FVW 48:;>D5=0:C C A8=>2V0;L=V9 @V48=V 28IV, =V6 C ?;072V, V 70;8H0NBLAO =0 28I8E @V2=OE ?@>BO3>< 12 3>48=.

@81;87=> ?>;>28=0 2AVTW :V;L:>ABV 22545=>3> 48;;>D5=0:C =0B@VN ?V440TBLAO<5B01>;V73>
?@>E>465==O. #=0A;V4>: FL>3> @V2=V ?;>IV ?V4 :@82>N «:>=F5=B@0FVO/G0A» (AUC) ?VA;O
?5@>@0;L=>3> 01> @5:B0;L=>3> ?@89>D5=0:C =0B@VN ?@81;87=> C 420 @078 <5=HV AUC, O:0
A?>AB5@V30TBLAO ?VA;O ?0@5=B5@0;L=>3> 22545==O 5:2V20;5=B=>W 4>78.
V>B@0=AD>@<0FVO 48;;>D5=0:C 2V41C20TBLAO G0AB:>2> 70 4>?><>3>N 3;N:C@>=C20==O V
<5B>:A8;N20==O. 20 7 28=8:0NG8E ?@8 FL>;L=8E <5B01>;V7>20=>2GN V :0;>
<5=H>N N, =V6 A0< 48;;>D5=0:.

8;;>D5=0: 282>48BLAO V7 ?;07<8 :@>2V 7 @V2=5< A8AB5<=>3> ;;V@5=AC 263 ± 56 <;/E2 (A5@54=V9
@V25=L ± AB0=40@B=5 2V4E8;5==O). V=F5289 T_{1/2} ?@5?0@0BC AB0=>28BL 1-2 3>48=8. @81;87=> 60
% 22545=>W 4>78 ?@5?0@0BC 282>48BLAO =8@:0<8 C 283;04V <5B01>;V7>20=>2GN V :0;>
4>78, I> ;8H8;0AO, 282>48BLAO C <5B01>;V7>20=>2GN V :0;>
=0G=8E 2V4AB59 2 01A>@1FVW, <5B01>;V7 2V4 2V:C ?0FVT=BV2 =5 A?>AB5@V30;>AO.
?0FVT=BV2 7 ?>@CH5==O<8 DC=:FVW =8@>: ?VA;O 70AB>AC20==O 728G09=>W 4>78 ?@5?0@0BC
=5 A?>AB5@V30;>AO 1C4L-O:>3> 71V;LH5==O :V;L:>ABV =5B> 48;;>D5=0:C. /:I> ;;V@5=A
:@50B8=V=C 1C2 =86G5 10 <;/E2, @>7@0EC=:>289 @V25=L <5B01>;V7>20=>2GN V :0;>
4 @078 28I89, =V6 C ?0FVT=BV2 7 =>@<0;L=>N DC=:FVTN =8@>:. 572060NG8 =0 F5, C :V=F52>2GN.
28?04:0E ?>@CH5=L DC=:FVW ?5GV=:8 (E@>=VG=89 35?0B8B, :>20=89 F8@>7 ?5GV=:8) D0@
<0:>:V=5B8:0 V <5B01>;V7< ?@5?0@0BC =5 2V4@V7=ONBLAO 2V4 B0:8E C ?0FVT=BV2 7 =>@
<0;L=>N DC=:FVTN ?5GV=:8.

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

A=>2=V DV78:>-EV 2;0AB82>ABV: ?@>7>@89 15710@2=89 01> 7V 7;53:0 6>2BC20B8< 2V4BV=:<<
@>7G8=.

5AC 5 7T:FV9.

"5@ABV.2 @>:8.

#<>28 715@V30==O. 15@V30B8 2 >@83V=0;L=V9 C?0:>2FV ?@8 B515@V30B8 C =54>ABC?=>

#?0:>2:0. >7G8= 4;O V= T:FV9 ?> 2<; 2 010 C :>@>1FV; 5E2, 10 C 1;VAB5@V C :>@>1FV.

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

8@>1=8:. "«\$0@<0F52B8G=0 :>@>2□O».

VAF57=0E>465==O.#:@0W=0, 61013,