

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

(DACARBAZINE MEDAC)

!::04:

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

1 D;0:>= 40:0@1078=C F8B@0B C ?5@5@0EC20==V =0 40:0@1078= 100 <3, 01> 200 <3, 01> 500 <3, 01> 1000 <3;

4>?>28=8: :8A;>B0 ;8<==0 1572>4=0, <0=VB (421).

V:0@AL:0 D>@<0. >@>H>: 4;O ?@83>BC20==O @>7G8=C 4;O V=T:FV9 01> V=DC7V9.

\$0@<0:>B5@0?52B8G=0 3@C?0. =B8=5>?;0AB8G=V 70A>18. ;:V;CNGV A?>;C:8.

>4 " ! L01A X04.

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

>:070==O.

A:;04V :><1V=>20=>W EVB5@0?VW:

E2>@>10 %>46:V=0;

?@>3@5ACNG0 A0@:><0 <O:8E B:0=8= (:@V< <57>B5;V><8, A0@:><8 0?>HV) C 4>@>A;8E.

@>B8?>:070==O.

V?5@GCB;82VABL 4> 40:0@1078=C 01> 4> 1C4L-O:>W V=H>W A:;04>2>W ?@5?0@0BC;

?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N;

;59:>?5=VO B0/01> B@><1>F8B>?5=VO;

BO6:0 ?5GV=:>20 B0/01> =8@:>20 =54>AB0B=VABL.

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

0AB>A>2C20B8 2=CB@VH=L>25==>. "5@0?VN <0T ?@>2>48B8 ;V:0@, O:89 <0T 4>A2V4 @>1>B8 2
>=:>;>3VW B0 35<0B>;>3VW.

0:0@1078= GCB;8289 4> 4VW A>=OG=>3> A2VB;0. AV @>7G8=8 40:0@1078=C<0NBL 1CB8 70E8I5=V
2V4 4VW A2VB;0, 0 B0:>6 V ?V4 G0A 22545==O (ABV9:89 4> A2VB;0 V=DC7V9=89 =01V@).

2545==O A;V4 ?@>2>48B8 4C65 >15@56=>, C=8:0NG8 ?>B@0?;O==O @>7G8=C 40:0@1078=C C
B:0=8=8, 0465 F5 <>65 A?@8G8=OB8 ?>H:>465==O B:0=8= B0 1V;L C 5:AB@02070FVO 2V41C;0AO,
22545==O A;V4 =5309=> ?@8?8=8B8, 0 70;8H>: 4>78 225AB8 2 V=HC 25=C.

;>O:VA=0 <5;0=><0.

@8 <=>B5@0?VW 40:0@1078= ?@87=0G0NBL, O: ?@028;>, C 4>7V 200-250 <3/<2 ?>25@E=V BV;0 C
283;04V 2=CB@VH=L>25==>W V=T:FVW 1 @07 =0 4>1C ?@>BO3< 5 4V1, ?>2B>@=V :C@A8 :>6=V 3
B86=V.

/: 0;LB5@=0B82C 2=CB@VH=L>25==V9 1>;NA=V9 V=T:FVW @>7G8= 40:0@1078=C <>6=0 22>48B8
A?>A>1< :>@>B:>B@820;>W V=DC7VW (?@>BO3< 15-30 E2).

"0:>6 <>6;82> ?@87=0G0B8 40:0@1078= O: 2=CB@VH=L>25==C V=DC7VN C 4>7V 850 <3/<2 1 @07 =0
4>1C V ?>BV< 1 @07 :>6=V 3 B86=V.

%2>@>10 %>46:V=0.

0:0@1078= ?@87=0G0NBL C 4>7V 375 <3/<2 ?>25@E=V BV;0 =0 4>1C (2=CB@VH=L>25==>) :>6=V 15
4V1. # FL>A>2CNBL C :<1V=0FVW 7 4>:A>@C1VF8=><, 1;5< B0 2V=1;0AB8=>< (ABVD @568<
4>7C20==O).

/0@:><0 <O:8E B:0=8= C 4>@>A;8E.

;O ;V:C20==O A0@:><8 < O:8E B:0=8= C 4>@>A;8E 0:0@1078= ?@87=0G0NBL C 4>7V 250 <3/<2 =0
4>1C 2=CB@VH=L>25==> (1-5 4=V2) C :<1V=0FVW 7 4>:A>@C1VF8=>< :>6=V 3 B86=V (ADIC).

V4 G0A B5@0?VW 40:0@1078=<?>B@V1=> @>18B8 ?5@V>48G=C ?5@52V@:C ?>:07=8:V2 :@>2V,
DC=:FV>=0;L=>3> AB0=C =8@>: B0 ?5GV=:8. A:V;L:8 G0AB> A?>AB5@V30NBLAO @50:FVW 7 1>:C
H;C=:>2>-.8H:>2>3> B@0:BC, @5:>5=4CTBLAO ?@>2>48B8 ?V4B@8A>2C20B8 ?@>B81;N20;L=V
70A>18.
A:V;L:8 <6CBL 28=8:=CB8 H;C=:>2>-.8H:>2V V 35<0B>;>3VG=V ?>@CH5==O, ?5@54 :>6=8< :C@A><
B5@0?VW 0:0@1078=>
"@820;VABL ;V:C20==O.
"@820;VABL ;V:C20==O ;V:0@ 287=0G0T V=482V4C0;L=> 4;O :>6=>3> 28?04:C, 2@0E>2CNG8 1030B>
D0:B>@V2 (B8? B0 AB04VO 70E2>@N20==O, :<1V=>20=0 B5@0?VO, ?>1VG=V 5D5:B8 B0
;V:C20;L=89 5D5:B, O:V A?@8G8=OT 40:0@1078= B>I>). # 28?04:C E2>@>18 %>46:V=0 70728G09= @5:>
<5=4CTBLAO ?@>25AB8 6 F8;;V2 ABVD :<1V=>20=>W B5@0?VW. # 28?04:C A0@:>8 <O:8E B:0=8=
B0 7;>O:VA=>W <5;0=>8 B@820;VABL ;V:C20==O 287=0G0TBLAO 5D5:B82=VABN 40:0@1078=C B0
B>;5@0=B=VABN 4> =L>3> ?0FVT=B0.
(284:VABL 22545==O.
>78 <5=HV 70 200 <3/<2 <6=0 ?>2V;L=> 22>48B8 O: 2=CB@VH=L>25==C V=T:FVN. V;LHV 4>78
40:0@1078=C (2V4 200 4> 850 <3/<2) A;V4 22>48B8 O: 2=CB@VH=L>25==C V=DC7VN ?@>BO3< 15-30
E2.
5:>5=4CTBLAO A?>G0B:C ?5@52V@8B8 ?@>EV4=VABL AC48=8 H;OE< 22545==O 5-10 <; 0,9 %
@>7G8=C =0B@VN E;>@84C 4;O V=DC7V9 01> 5 % @>7G8=C 3;N:>78. &V 6 A07G8=8
28:>@8AB>2CNBL 4;O ?@<820==O D;0:>=0 ?VA;O V=T:FV9 2V4 70;8H:>28E :V;L:>AB59 ?@5?0@0BC.
@8 @>7G8=5==V C 2>4V 157 ?>40;LH>3> @>72545==O 0,9 % @>7G8=< =0B@VN E;>@84C 4;O
V=T:FV9 01> 5 % @>7G8=< 3;N:>78 >45@60=89 @>7G8= ?@5?0@0BC (100 01> 200 <3 40:0@1078=C) T
3V?>>A<;O@=8< (100 <A<;L/:3), B>3> A;V4 22>48B8 ?>2V;L=>, ?>=04 1 E2, 703> 1>;NA=>3>
2=CB@VH=L>25==>3> 22545==O 70 :V;L:0 A5:C=4.
0FVT=B8 7 =8@:>2>N B0 ?5GV=:>2>N =54>AB0B=VABN.
/:I> C ?0FVT=B0 ;8H5 =57=0G=5 ?>@CH5==O DC=:FVW =8@>: 01> ?5GV=:8, :>@83C20==O 4>78
=5>1>2O7:>25. # E2>@8E V7 :<1V=>20=>N =8@:>2>N B0 ?5GV=:>2>N =54>AB0B=VABN
71V;LHCTBLAO G0A 282545==O 40:0@1078=C. @>B5 4>AV =5<0T =VO:8E 70B25@465=8E @5:>
<5=40FV9 I>4> 7<5=H5==O 4>78 4;O B0:8E E2>@8E.
N48 ;VB=L>3> 2V:C.
5<0T =VO:8E @5:>5=40FV9 I>4> 70AB>AC20==O 40:0@1078=C ;N4O< ;VB=L>3> 2V:C, >A:V;L:8
2V4ACB=V9 4>AB0B=V9 4>A2V4 70AB>AC20==O FL>3> ?@5?0@0BC 40=V9 :0B53>@VW
?0FVT=BV2.
54V0B@8G=0 ?@0:B8:0.
>:8 I> 2V4ACB=O 4>AB0B=O :V;L:VABL V=D>@<0FVW I>4> 70AB>AC20==O 40:0@1078=C C
?54V0B@VW.
@83>BC20==O @>7G8=C 4;O 2=CB@VH=L>25==>3> 22545==O.
>7G8= 3>BC20B8 157?>A5@54=L> ?5@54 22545==O<, 28:>@8AB>2C20B8 =5309=>.
0:0@1078= GCB;8289 4> A>=OG=>3> A2VB;0, B>18 4;O ?@83>BC20==O B0 22545==O @>7G8=C
=5>1EV4=> 70E8I0B8 2V4 A2VB;0, =0?@8;;04 A8AB5<8 4;O 2;820==O 7 ?>;V2V=V;E;>@84C, ABV9:V 4>
A2VB;0.
@8 28:>@8AB0==V 728G09=8E A8AB5< 4;O 2;820==O WE A;V4 >13>@B0B8 #S-ABV9:>N D>;L3>N.
a) @83>BC20==O @>7G8=C 40:0@1078=C (4>7C20==O 100 <3 B0 200 <3):
A5?B8G=> 2=>A8B8 ?>B@V1=C :V;L:VABL 2>48 4;O V='T:FV9 (40:0@1078= 100<3 C 10 <;, 200 <3 C 20
<.) C D;0:>= 7 ?@5?0@0B< V AB@CHC20B8 4> ?>2=>3> @>7G8=5==O. !2V6>?@83>B>2;5=89 @>7G8=
22>48B8 O: ?>2V;L=C V=T:FVN.
;O 2=CB@VH=L>25==>W V=DC7VW >45@60=89 A2V6>?@83>B>2;5=89 @>7G8= @>72>48B8 C 200-
300 <;
0,9 % @>7G8=C =0B@VN E;>@84C 4;O V=T:FV9 01> 5 % @>7G8=C 3;N:>78. &59 @>7G8= 2>4OBL O:
:>@>B:>B@820;C 2=CB@VH=L>25==C V=DC7VN ?@>BO3< 15-30 E2.
b) @83>BC20==O @>7G8=C 40:0@1078=C (4>7C20==O 500 <3 B0 1000 <3):

A5?B8G=> 2=>A8B8 50 <; 2>48 4;O V='T: FV9 C D;0:>= 7 ?@5?0@0B< V AB@CHC20B8 4> ?>2=>3>
@>7G8=5==O. 45@60=89 @>7G8= @>72>48B8 C 200-300 <; 0,9 % @>7G8=C =0B@VN E;>@84C 4;O
V=T: FV9 01> 5 % @>7G8=C 3;N:>78. &59 @>7G8= 22>48B8 O: 2=CB@VH=L>25==C V=DC7VN
?@>BO3<<
20-30 E2.
>@>H>: 40:0@1078=C <>6=0 28:>@8AB>2C20B8 ;8H5 >4=>@07>2>. 5@54 22545==O< @>7G8=
2V7C0;L=> ?5@52V@OB8, 28:>@8AB>2C20B8 ;8H5 ?@>7>@89, ?@0:B8G=> 2V;L=89 2V4
=5@>7G8=5=8E G0AB8=>: @>7G8=.
C4L-O:C G0AB8=C 2=0, I> 70;8H0TBLAO ?VA;O ?@83>BC20==O @>7G8=C A;V4 7=8IC20B8, B0: A0<>
O: V @>7G8=8, I> =5 ?@>9H;8 2V7C0;L=>W ?5@52V@:8.
#AV<0B5@V0;8, I> 28:>@8AB>2C20;8AO ?@8 283>B>2;5==V B0 22545==V @>7G8=C, =5>1EV4=>
CB8;V7>2C20B8 (A?0;N20B8).

>1VG=V @50:FVW.
>1VG=V @50:FVW :;0A8DV:CNBLAO 70 G0AB>B>N 28=8:=5==O:
4C65 ?>H8@5=V (□ 1/10), ?>H8@5=V (□ 1/100, □ 1/10), =5?>H8@5=V (□ 1/1 000, □ 1/100), @V4:>
?>H8@5=V (□ 1/10 000, □ 1/1 000), 4C65 @V4:> ?>H8@5=V (□ 1/10 000), 2::NG0NG8 ?>>48=>:V 28?04:8.
I>:C :@>2>=>A=>W B0 ;VW A8AB5 ?>H8@5=V 0=5?5=VO, B@><1>F8B>?5=VO; @V4:> ?>H8@5=V
?0=F8B>?5=VO, 03@0=C;>F8B>7. AB0==V 70;560BL 2V4 4>78 V 2V4AB@>G5=V, 7 =87L:>N
G0AB>B>N, I> 28=8:0NBL ?VA;O 3-4 B86=O.
I>:C VW A8AB5<8: @V4:> ?>H8@5=V 0=0DV;0:B8G=V @50:FVW.
I>:C =5@2>2>W A8AB5<8: @V4:> ?>H8@5=V 3>;>2=89 1V;L, ?>3V@H5==O 7>@C, A?;CB0=VABL
A2V4><>ABV, AC4<8, ?0@5AB57VO >1;8GGO.
!C48==V ?>@CH5==O: @V4:> ?>H8@5=V ?@8?;828.
I>:C H;C=:>2>-.8H:>2>3> B@0:BC: ?>H8@5=V 0=>@5:AVO, =C4>B0, 1;N20==O; @V4:> ?>H8@5=V
4V0@5O.
5?0B>1V;V0@=V ?>@CH5==O: @V4:> ?>H8@5=V>1AB@C:FVO ?5GV=:>2>W 25=8 4> =5:@>7C
?5GV=:8, 71V;LH5==O 0:B82=>ABV ?5GV=:>28E D5@<5=BV2.
!5G>284V;L=0 A8AB5<0: @V4:> ?>H8@5=V =8@:>20 =54>AB0B=VABL.
(:V@0 B0 H:V@=V ?@840B:8: =5?>H8@5=V 0;>?5FVO, 3V?5@?V3<5=B0FVO, D>B>A5=A81V;V70FVO;
@V4:> ?>H8@5=V 5@8B5<0, <0:C;>?0?C;L>7=0 5:70=B5<0, :@>?82O=:0.
030;L=V V @CH5==O: =5?>H8@5=V 3@8?>?>4V1=89 A8=4@<; @V4:> ?>H8@5=V 70?0;5==O C
01>@0B>@=V ?>:07=8:8: @V4:> ?>H8@5=V ?V428I5==O @V2=O ?5GV=:>28E 5=78
>@CH5==O B@02=>3> B@0:BC, B0:V O: 0=>@5:AVO, =C4>B0, 1;N20==O 7030;L=V V BO6:V. #
@V4:8E 28?04:0E A?>AB5@V30;0AL 4V0@5O.
'0AB> A?>AB5@V30;8AO 72V (0=5?5=VO, B@><1>F8B>?5=VO) 4>7>70;56=V V 2V4AB@>G5=V, 7
=87L:>N G0AB>B>N, I> 28=8:0NBL ?VA;O 3-4-3> B86=O. C;8 >?8A0=V @V4:> ?>H8@5=V 28?04:8
?0=F8B>?5=VW V 03@0=C;>F8B>7C.
VA;O 70AB>AC20==O 40:0@1078=C A?>AB5@V30;8AO 3@8?>?>4V1=89 A8=4@< V7 2B><>N, >7=>1>
<, 30@OG:>N V <□O7>28< 1>;5
V4:> <>65 A?>AB5@V30B8AO ?V428I5==O 0:B82=>ABV ?5GV=:>28E D5@<5=BV2 (=0?@8:;04 ;C6=>W
D>AD0B078).
V4 G0A <>=>B5@0?VW 40:0@1078=<< 01> C :<<1V=>20=V9 B5@0?VW @V4:> A?>AB5@V302AO
=5:@>7 ?5GV=:8 2=0A;V4>: 70:C?>@5==O 2=CB@VH=L>?5GV=:>28E 25= (25=>->1;VB5@CNG0
E2>@>10 ?5GV=:8), O:89 28=8:02 ?@>BO3<< 4@C3>3> F8;;C ;V:C20==O. 0;8 78=>DV;VO, 1V;L C
682>BV, 71V;LH5==O ?5GV=:8, 6>2BO=8FO V H>: !8<8 ?@>3@5AC20;8 ?@>BO3<< :V;L:>E 3>48= 01>
4=V2. A:V;L:8 1C;8 ?>2V4<;5==O ?@> ;5B0;L=89 =0A;V4>;, A;V4 C206=> V G0AB> ?5@52V@OB8 @>7
6 ?@>2>48B8 0=0;V7 :@>2V (>A>1;82> 278=>DV;V2). # ?>>48=>:8E 28?04:0E ?@8 ?V4>7@V =0 25=>-
>1;VB5@CNGC E2>@>1C 1C;0 CA?VH=>N B5@0?VO 7 28A>:>N 4>7>N :>@B8:>AB5@>W4V2
(=0?@8:;04 3V4@>:>@B87>= 300 <3 =0 4>1C) 01> 157 DV1@8=>;VB8G=8E 035=BV2, ?>4V1=8E 4>
35?0@8=C 01> B:0=8==8E 0:B820B>@V2 ?;0735=C.
>4@07=5==O B0 45O:V ?>1VG=V @50:FVW, I> 28=8:0NBL C< D>@4C:BV2 D>B>453@040FVW.
V4:> A?>AB5@V30;>AO ?>@CH5==O DC=:FVW =8@>: 7 ?V428I5==O< C :@>2V :>=F5=B@0FVW
@5G>28=, O:V 282>4OBLAO 7 A5G5N.

V4:> <>6CBL A?>AB5@V30B8AO ?>1VG=V 5D5:B8 7 1>:C F5=B@0;L=>W =5@2>2>W A8AB5<8, B0:V
O: 3>;>2=89 1V;L, ?>@CH5==O 7>@C, 30;NF8=0FVW, A>;82VABL V AC4<8.
VA;O V= T:FVW <>6CBL A?>AB5@V30;8AO ?0@5AB57VO V ?@8?;828.
C65 @V4:> <>6CBL A?>AB5@V30B8AO 0;5@3VG=V @50:FVW =0 H:V@V, B0:V O: 5@8B5<0,
<0:C;>?0?C;L>7=0 5@8B5<0 01> :@>?82O=:0.
5G0AB> <>6CBL A?>AB5@V30B8AO 0;>?5FVO, 3V?5@?V3<5=B0FVO V D>B>GCB;82VABL H:V@8.
C;8 >?8A0=V @V4:V 28?04:8 0=0DV;0:B8G=8E @50:FV9.
0@025=>7=0 V= T:FVO <>65 ?@8725AB8 4> 3> 1>;N V =5:@>7C.

5@54>7C20==O.

5@H8<8 >GV:C20=8<8 CA;;04=5==O<8 ?@8 ?5@54>7C20==V 40:0@1078=C T ?@83=VG5==O DC=:FVW
:VAB:>2>3> <>7:C, 7@5HB>N 0?;07VO :VAB:>2>3> <>7:C, O:0 28=8:0T G5@57 2 B86=V. <5=H5==O
@V2=O ;59:>F8BV2 B0 B@><1>F8BV2 <>65 A?>AB5@V30B8AO =0 4- ?5@54>7C20==O ;8H5
?V4>7@NTBLAO, =5>1EV4=> ?@>2>48B8 4>23>B@820;89 <=>VB>@8=3 ?>:07=8:V2 :@>2V ?0FVT=B0.
5 A;V4 4>?CA:0B8 ?5@54>7C20==O 40:0@1078=>B =52V4><89.

0AB>AC20==O 2 ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.

4>A;V40E =0 B20@8=0E 40:0@1078= 28O282 35==C V :0=F5@>35==C 4VN. # ;N48=8 B0:>6 VA=CT
@878: B5@0B>35==>W 4VW.
0:0@1078= =5 <>6=0 70AB>A>2C20B8 C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N.
>B5=FV9=89 @878: 4;O 6V=>: @5?@>4C:B82=>3> 2V:C: A;V4 C=8:0B8 203VB=>ABV ?V4 G0A
;V:C20==O 40:0@1078=>

VB8.

0:0@1078= =5 @5:><5=4CTBLAO 4;O 70AB>AC20==O 4VBO<, 2@0E>2CNG8 =54>AB0B=N :V;L:VABL
40=8E I>4> 70AB>AC20==O ?@5?0@0BC FV9 :0B53>@VW ?0FVT=BV2.

A>1;82V 70E>48 157?5:8.

!;V4 4>B@81V6=8E 70E>4V2 ?@8 @>1>BV 7 F8B>AB0B8G=8<8 ;V:0@AL:8<8 70A>10<8, I> <0NBL
B5@0B>35==89, 35==89 5D5:B.
0:0@1078= ?@>B8?CE;8==89 035=B. 5@H =V6 2V4:@8B8 D;0:>=, =5>1EV4=> >7=09><8B8AO 7 ?@028;0
<8 @>1>B8 7 F8B>AB0B8:0<8.
0:0@1078= <>6CBL 2V4:@820B8 ;8H5 4>A2V4G5=V >A>18, V B0: A0<>, O: V C 2AVE 28?04:0E @>1>B8
7 F8B>AB0B8:0<8, A;V4 C=8:0B8 2?;82C ?@5?0@0BC =0 ?5@A>=0;. # ?5@V>4 203VB=>ABV A;V4
C=8:0B8 1C4L-O:>3> :>=B0:BC 7 F8B>AB0B8:0<8. @83>BC20==O @>7G8=C ?@>2>48B8 C A?5FV0;L=>
A><, O:89 <>6=0 <8B8, 01> =04 04A>@1CNG8< ?0?5@><, ?V4 O:89 ?V4AB8;0B8 ?;0AB8:>2C ?V4AB8;;C.
>B@V1=> 24O30B8 2V4?>2V4=V 70E8A=V >:C;O@8, @C:028G:8, <0A:C =0 >1;8GGO B0 D0@BCE.
(?@8F8 B0 70A>18 4;O 22545==O A;V4 @5B5;L=> 718@0B8, I>1 70157?5G8B8 WE 35@<5B8G=VABL B0
C=8:=CB8 28BV:0==O @>7G8=C ?@5?0@0BC.
@8 ?>B@0?;O==V @>7G8=C =0 1C4L-O:C ?>25@E=N WW A;V4 =5309=> @5B5;L=> 28<8B8, B0:>6 28
<8B8 @C:8 B0 >1;8GGO.
@07V 28BV:0==O @>7G8=C @V48=C ?@818@0B8 70 4>?<>3>N 04A>@1CNG>3> <0B5@V0;C.
>25@E=O, =0 O:C ?>B@0?82 @>7G8=, <8B8, C25AL :>=B020=89 <0B5@V0; ?V4;O30T CB8;V70FVW
(A?0;N20==N).

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

"5@0?VN <0T ?@>2>48B8 4>A2V4G5=89 ;V:0@ >=:>;>3-35<0B>;>3 C <548G=8E 70;;040E, 45 T
<>6;82VABL ?5@52V@8B8 ;;V=VG=V, 1V>EV
/I> 7O28;8AO @50:FVW 3V?5@GCB;82>ABV 01> DC=:FV>=0;L=0 =8@:>20 G8 ?5GV=:>20
=54>AB0B=VABL, A;V4 =5309=> ?@8?8=8B8 ;V:C20==O 40:0@1078=>A?>AB5@V30NBLAO >;N782=V
70E2>@N20==O ?5GV=:>28E 25=, ?>40;LH5 ;V:C20==O F8< ?@5?0@0B< ?@>B8?>:070=5.
@8 V:0@<0T 7=0B8 ?@> B06:5 CA;;04=5==O B5@0?VW (I> @V4:> 7CAB@VG0TBLAO V T =0A;V4:<
=5:@>7C ?5GV=:8), >1C<>2;5=5 70:C?>@N20==O< 2=CB@VH=L>?5GV=:>28E 25=. ">1EV4=>
?@>2>48B8 ?5@V>48G=89 :>=B@>;L @>72V (>A>1;82> @V25=L 5>78=>DV;V2). # 45O:8E 28?04:0E
?@8 ?V4>7@V =0 >1AB@C:FVN 25= T 5D5:B82=>N @0==O B5@0?VO 28A>:8<8 4>70<8

:>@B8:>AB5@>W4V2 (=0?@8:;04 3V4@>:>@B87>= 300 <3 =0 4>1C) 7 01> 157 35?0@8=C G8 B:0=8==8E
0:B820B>@V2 ?;0735=C.

"@820;0 B5@0?VO <>65 A?@8G8=8B8 :C:A8G=C 4VN =0 :VAB:>289<>7>:.

@0E>2CNG8 <>6;825 ?@83=VG5==O DC=:FVW :VAB:>2>3><>7:C, =5>1EV4=> ?5@V>48G=>

?@>2>48B8 ?5@52V@:C @V2=O ;59:>F8BV2, 5@8B@>F8BV2 B0 B@><1>F8BV2 C :@>2V.

@83=VG5==O 35<>?>57C <>65 1CB8 ?V4AB02>N 4;O B82>3> 01> >AB0B>G=>3> ?@8?8=5==O

B5@0?VW F8< ?@5?0@0B>25==>3> 22545==O ?@872>48BL 4> CH:>465==O B:0=8= B0 A8;L=>3> 1>;N.

0:0@1078= T VAC?@5A0=B<< A5@54=L>W V=B5=A82=>ABV.

@>BO3<< B5@0?VW 40:0@1078=<< =5>1EV4=> CB@83>;N B0 35?0B>B>:A8G=8E ?@5?0@0BV2.

'>;>2V:0< @5:<<5=4CTBLAO :>@8ABC20B8AO =04V9=8<8 70A>10<8 :>=B@0F5?FVW ?@>BO3<<

;V:C20==O B0 ?@>BO3<< 6

**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.**

0:0@1078= <>65 2?;820B8 =0 740B=VABL :5@C20B8 02B<>1V;5< 01> ?@0FN20B8 7V A:;04=8<8

<5E0=V7<0<8 G5@57 ?>1VG=V @50:FVW 7 1>:C F5=B@0;L=>W =5@2>2>W A8AB5<8, =C4>BC B0

1;N20==O.

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

@07V ?>?5@54=L>3> 01> AC?CB=L>3> ;V:C20==O ?@5?0@0B0<8, I> G8=OBL =5A?@8OB;82C 4VN

=0 :VAB:>289<>7>: (F8B>AB0B8G=V 035=B8, @04V>B5@0?VO), <>6;825 ?>A8;5==O B>:A8G=>ABV

0:0@1078=C <540:.

82G5==O <5B01>;V72>48;>AO, 0;5 2V4><>, I> 3V4@>:A8;C20==O 28EV4=>W @5G>28=8 A?@8OT

?V4A8;5==N WW ?@>B8?CE;8==>W 4VW. 0:0@1078= <5B01>;V7CTBLAO C ?5GV=FV 70 4>?<>3>N

P450 (CYP1A1, CYP1A2 B0 CYP2E1). &5 =5>1EV4=> 2@0E>2C20B8 C @07V >4=>G0A=>3>

?@87=0G5==O ;V:0@AL:8E 70A>1V2, I> <5B01>;V7CNBLAO F8<8 6 D5@<5=B0<8.

0:0@1078= <>65 ?V4A8;N20B8 D>B>A5=A81V;V7CNGC 4VN <5B>:A8?A>@0;5=C.

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

\$0@<0:>48=0.

0:0@1078= 0;;V;CNG89 F8B>AB0B8G=89 70AV1 B@8075=>2>W AB@C:BC@8.

5E0=V7< 4VW ?>;O30T C ?@83=VG5==V @>ABC ;VB8= (I> =5 ?>2O70=> 7 ;VB8==8< F8;:<B0 2

V=3V1C20==V A8=B57C . 0:0@1078= B0:>6 <0T 0;;V;CNG89 5D5:B B0 <>65 2;;NG0B8AO 2 V=HV

F8B>AB0B8G=V <5E0=V7<8.

2060TBLAO, I> A0< 40:0@1078= =5 <0T 0=B8=5>;0AB8G=>3> 5D5:BC, 0;5 2 @57C;LB0BV A><0;L=>3>

N-45<5B8;C20==O 2V= H284:> ?5@5B2>@NTBLAO =0 5-0-V;-4-:0@1>:A0

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

VA;O2=CB@VHL>25==>3> 22545==O 40:0@1078= H284:> ?@>=8:0T C B:0=8=8. 2O7C20==O 7 1V;;0<8

?;07<8 :@>2V AB0=>28BL 5 %. V=5B8:0 C ?;072V 42>D07>20, 7 ?>G0B:>28< ?5@V>4<<

=0?V2282545==O 20 E28;8= B0 B5@P450, I> ?@872>48BL 4> CB2>@5==O 0:B82=8E N-45<5B8;L>20=8E

A?>;C: " ! B0 " !. &59 ?@>F5A :0B0;V7CTBLAO D5@<5=B0<8 CYP1A1, CYP1A2 B0 CYP2E1.

" ! =040;V <5B01>;V7CTBLAO 4> 5-0-V;C-4-:0@1>:A0

>;:V=VG=V 40=V 157?5:8

0:0@1078= 28O2;OT 35==V V B5@0B>35==V 5D5:B8, O:V 1C;8 28O2;5=V C E>4V 5:A?5@8<5=B0;L=8E

4>A;V465=L.

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

A=>2=V DV78:>-EVABV:

1V;89 01> A2VB;>-6>2B>3> :>;L>@C ?>@>H>: 01> A?5G5=0 <0A0.

5AC.

0:0@1078= 70 EVN AB@C:BC@>N =5AC<, 3V4@>:>@B87>=<<, L-F8AB5W=<< V =0B@VN

3V4@>35=:0@1>=0B>

"5@ABV. 3 @>:8.

"5@ABV 2V4=>2;5=>3> @>7G8=C: EVBO3><
24 3>48= ?@8 B5 C 70E8I5=>
1V>;>3VG=>W B>G:8 7>@C @>7G8= =5>1EV4=> 28:>@8AB0B8 =5309=>. /:I> @>7G8= =5 1C2
28:>@8AB0=89 =5309=>, :>@8ABC20G =5A5 2V4?>2V40;L=VABL 70 B@820;VABL V &>28
715@V30==O, O:V =5 <0NBL ?5@528IC20B8 24 3>48=8 B0 B58 °C, O:I> @>72545==O ?@>2>48;8 C
:>=B@>;L>20=8E V 20;V4>20=8E 0A5?B8G=8E C<>20E.
V4=>2;5=89 V 2 ?>40;LH>72545=89 @>7G8= A;V4 28:>@8AB0B8 =5309=>.

#<>28 715@V30==O.
15@V30B8 ?@8 B5°! C =54>ABC?=>@83V=0;L=V9 C?0:>2FV 4;O 70E8ABC 2V4 A2VB;0.

#?0:>2:0.
@5?0@0B ?>=8 (B8?). \$;0:>=8, I> ==V C?0:>2:8 10, D;0:>=8 ?> 500 <3 B0 1000 <3 40:0@1078=C ?>==V
C?0:>2:8 1. >6=0 C?0:>2:0

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

8@>1=8:.
<540: <1%/medac GmbH.

VAF57=0E>465==O.
\$5;0=4HB@0AA5, 3, -20354 0<1C@3, V<5GG8=0/Fehlandtstrasse, 3, D-20354 Hamburg, Germany.