

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

&□ !®
(CEDAX□)

!,:04:

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

5 <; 3>B>2>W ACA?5=7VW

4>?>28=8: ?>;VA>@10B 80, A8<5B8:>=, :A0=B0=>20 :0<54L, :@5<=VN 4V>:A84, B8B0=C 4V>:A84
(171), =0B@VN 15=7>0B (211), 0@><0B870B>@ 28H=O, A0E0@>70.

V:0@AL:0 D>@<0. >@>H>: 4;O >@0;L=>W ACA?5=7VW.

\$0@<0:>B5@0?52B8G=0 3@C?0. =B810:B5@V0;L=V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O.
?>A?>@8=8. >4 "I J01D D14.

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

>:070==O.

>@>A;8

V:C20==O V=D5:FV9, A?@8G8=5=8E GCB;828<8 4> ?@5?0@0BC >@30=V7<0<8:

□ V=D5:FVW 25@E=VE 48E0;L=8E H;OEV2 B0 ->@30=V2, 2;;NG0NG8 D0@8=3VB, B>=78;VB,
A:0@;0B8=0, 3>AB@89 A8=CA8B;

□ V=D5:FVW =86=VE 48E0;L=8E H;OEV2, 2;;NG0NG8 3>AB@89 1@>=EVBC, 703>AB@5==O
E@>=VG=>3> 1@>=EVBC B0 3>AB@C ?=52<=>VN, C 28?04:0E, :>;8 <>6;820 ?5@>@0;L=0 B5@0?VO,
B>1B> ?@8 =53>A?VB0;L=8E V=D5:FVOE;

□ V=D5:FVW A5G>282V4=8E H;OEV2, C B>
VBO

V:C20==O V=D5:FV9, A?@8G8=5=8E GCB;828<8 4> ?@5?0@0BC >@30=V7<0<8:

□ V=D5:FVW 25@E=VE 48E0;L=8E H;OEV2 B0 ->@30=V2, 2;;NG0NG8 D0@8=3VB, B>=78;VB,
A:0@;0B8=0, A5@54=V9 >B8B;

□ V=D5:FVW A5G>282V4=8E H;OEV2, C B>

□ 5=B5@8B B0 30AB@>5=B5@8B, A?@8G8=5=89 Salmonella, Shigella01> E. Aoli.

@>B8?>:070==O.

V428I5=0 GCB;82VABL 4> F5D0;>A?>@8=V2 01> 4> 1C4L-O:>W 4>?>W @5G>28=8.

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

"@820;VABL ;V:C20==O &545:A<, O: V V=H8<8 ?5@>@0;L=8<8 0=B81V>B8:0<8, 70728G09
AB0=>28BL 5-10 4=V2. @8 ;V:C20==V V=D5:FV9, A?@8G8=5=8E Streptococcus pyogenes, &545:A C
B5@0?52B8G=V9 4>7V 70AB>A>2CNBL ?@>BO3< I>=09<5=H5 10 4=V2.

>@>A;V. 5:><5=4>20=0 4>70 &545:AC AB0=>28BL 400<3 =0 4>1C. @8 ;V:C20==V 3>AB@>3>
10:B5@V0;L=>3> A8=CA8BC, 3>AB@>3> 1@>=EVBC, 703>AB@5==O E@>=VG=>3> 1@>=EVBC B0
CA:;04=5=8E 01> =5CA:;04=5=8E V=D5:FV9 A5G>282V4=8E H;OEV2 ?@5?0@0B 70AB>A>2CNBL ?>
400<3 1 @07 =0 4>1C. @8 ;V:C20==V =53>A?VB0;L=>W ?=52<=>VW C ?0FVT=BV2, O:8< 4>@5G=0
?5@>@0;L=0 B5@0?VO, @5:><5=4>20=0 4>70 AB0=>28BL 200<3 :>6=V 12 3>48=.

>@>A;V ?0FVT=B8 7 ?>@CH5=>N DC=:FVTN =8@>:. @8 ?>G0B:>2V9 =54>AB0B=>ABV =8@>: D0@
<0>:V=5B8:0 &545:AC VAB>B=> =5 7@83C20B8 4>78 ?>B@V1=> BV;L:8 ?@8 7=865==V ;V@5=AC
:@50B8=V=C <5=H5 50 <;/E2. /:I> ;V@5=A :@50B8=V=C AB0=>28BL 2V4 30 4> 49<;/E2, 4>1>2C 4>7C
A;V4 7<5=H8B8 4> 200<3. @8 ;V@5=AV :@50B8=V=C 2V4 5 4> 29<;/E2 @5:><5=4>20=0 4>1>20 4>70
AB0=>28BL 100<3.

@8 =5>1EV4=>ABV 7<5=H8B8 :@0B=VABL 70AB>AC20==O &545:AC C 4>7V 400<3 <>6=0
70AB>A>2C20B8 :>6=V 48 3>48= (G5@57 45=L) ?@8 ;V@5=AV :@50B8=V=C 30-49 <;/E2 B0
:>6=V

96 3>48= (G5@57 3 4=V) ?@8 ;V@5=AV :@50B8=V=C 5-29<;/E2.

%2>@8<, O:V >B@8
VB8 2V4 6 5:><5=4>20=0 4>70 &545:AC C 283;O4V ACA?5=7VW 4;O ?@89> AB0=>28BL 9 <3/:3/4>1C (<0:A8
VBO< 7 <0A>N BV;0 ?>=04 45 :3 01> AB0@H5 10 @>:V2 &545:A 70AB>A>2CNBL C @5:><5=4>20=V9 4;O 4>@>A;8E 4>7V.
!/?>AVI ?@83>BC20==O ACA?5=7VW.
5@54 ?@83>BC20==O< ACA?5=7VW A;V4 AB@CA8B8 D;0:>= V7 ?>@>H:>1EV4=C :V;L:VABL 2>48 (:V <=0B=>W B57CNGC A;;O=>G:C 4> @V2=O >B2>@C (28 <;) B0 4>40B8 42><0 @V2=8<8 ?>@FVO<8 4> D;0:>=0 7 ?>@>H:> AB@CHC20B8 D;0:>= ?VA;O :>6=>3> 4>4020==O 2>48 4;O @V2=>3> 7<>GC20==O B0 ?>2=>3> @>7G8=5==O ?>@>H:C. @8 ?@83>BC20==V B0:8< G8=>< CB2>@NTBLAO 30 <; ACA?5=7VW, O:0
5@54 ?@89><>< ?@5?0@0BC D;0:>= V7 ?@83>B>20=>N ACA?5=7VTN A;V4 V=B5=A82=> AB@CHC20B8.

>1VG=V @50:FVW.
::V=VG=8E 4>A;V465==OE, ?@>2545=8E 7 CG0ABN ?@81;87=> 3000 ?0FVT=BV2, =09G0ABVH8<8 ?>1VG=8<8 @50:FVO<8 1C;8 =C4>B0 (3 %), 4V0@5O (3 %) B0 3>;>2=89 1V;L (2 %).
@06=>W 3@C?8 G0AB>B8 =51060=V O28I0 =040=V C ?>@O4:C 7<5=H5==O BO6:>ABV.

51060=V O28I0, O:V 2V47=0G0;8AO ?V4 G0A :;V=VG=8E 4>A;V465=L 01> ?@8 ?>AB-<0@:5B8=3>2>AC20==V C ?0FVT=BV2, O:V ?@89<0;8 &!	
!8AB5<8 >@30=V2	>1VG=V @50:FVW
=D5:FVW B0 V=207VW	
5G0AB>:	:0=484>7 (@>B>2>W ?>@>6=8=8), 203V=0;L=V V=D5:FVW
V4:>:	:>;VB, A?@8G8=5=89 <i>Clostridium difficile</i>
52V4><>:	AC?5@V=D5:FVO
>@CH5==O 7 1>:C :@>2V B0 ;VW A8AB5<8	
5G0AB>:	5>78=>DV;VO, ?>78B82=0 ?@O<0 ?@>10 C<1A0*, 7=865==O @V2=O 35<>3;>1V=C, ?>4>265==O ?@>B@><1V=>2>3> G0AC /71V;LH5==O 4=>3> =>@<0;V7>20=>3> 2V4=>H5==O ()
V4:>:	;59:>?5=VO, B@><1>F8B5
>@CH5==O 7 1>:C VW A8AB5<8	
52V4><>:	A8@>20B:>20 E2>@>10; @50:FVW 3V?5@GCB;82>ABV 2:;NG0NG8 0=0DV;0:B8G=V @50:FVW, 1@>=E>A?07<, 28A8?0==O, :@>?82O=:0, @50:FVW D>B>GCB;82>ABV, A25@1V6, 0=3V>=52@>B8G=89 =01@O:, A8=4@>< !BV25=A0-6>=A>=0, @<=0 5@8B5<0 B0 B>:A8G=89 5?V45@<0;L=89 =5:@>;V7
>@CH5==O 7 1>:C =5@2>2>W A8AB5<8	
'0AB>:	3>;>2=89 1V;L
5G0AB>:	7
V4:>:	AC4><8
C65 @V4:>:	?0@5AB57VW, A>=;82VABL, 70?0 <>@>G5==O C 4VB59: 3V?5@:V=57

52V4><:	0D07VO
>@CH5==O 7 I>:C >@30=V2 A;CEC B0 ;01V@8=BC	
C65 @V4>:	25@B83>
A8EVG=V ?>@CH5==O	
C65 @V4>:	# 4VB59: 71C465==O, 157A>==O
52V4><:	?A8EVG=V ?>@CH5==O, ?A8E>7
>@CH5==O <5B0I>;V7	
5G0AB>:	0=>@5:AVO
>@CH5==O 7 I>:C 48E0;L=>W A8AB5<8	
5G0AB>:	70::045=VABL =>A0, 7048H:0
52V4><:	A28ABOG5 48E0==O
>@CH5==O 7 I>:C H;C=:>2>-:8H:>2>3> B@0:BC	
'0AB>:	=C4>B0, 4V0@5O (7/157 453V4@0B0FVW)
5G0AB>:	30AB@8B, 1;N20==O, 1V;L C 682>BV, 70?>@, ACEVABL C @>BV, 48A?5?AVO, <5B5>@87<, =5B@8<0==O :0;C
52V4><:	<5;5=0
>@CH5==O 7 I>:C ?5GV=:8 B0 6>2G>282V4=8E H;OEV2	
5G0AB>:	3V?5@1V;V@C1V=5B@0=AD5@078, ?V428I5==O @V2=O 0;0=V=0 B@0=AD5@078, ?V428I5==O @V2=V2 ;C6=>W D>AD0B078
V4> :	?V428I5==O @V2=O ;0:B0B453V4@>35=078 C :@>2V
52V4><:	70E2>@N20==O ?5GV=:8 B0 6>2G=>3> 2B0=8FO, ?5GV=:>289 E>;5AB07
>@CH5==O 7 I>:C H:V@8 B0 ?V4H:V@=>-68@>2>W B:0=8=8	
5G0AB>:	C 4VB59: ?5;NH:>289 45@<0B8B
>@CH5==O 7 I>:C A5G>284V;L=>W A8AB5<8	
5G0AB>:	487C@VO C 4VB59: 35<0BC@VO =8@:>20 =54>AB0B=VABL*, B>:A8G=0 =5D@>?0BVO*, =8@:>20 3;N:>7C@VO*, :5B>=C@VO*, ?V428I5==O @V2=V2 :@50B8=V=C B0 A5G>28=8
030;L=V ?>@CH5==O B0 @50:FVW C	
C65 @V4>:	?V428I5=0 2B><;N20=VABL, <548:0 <5=B>7=0 30@OG:0; C 4VB59: 4@0BV2;82VABL, >7=>1

* !?>AB5@V30TBLAO ?@8 70AB>AC20==V V=H8E F5D0;>A?>@8=V2 B0 <>65 28=8:=CB8 ?@8 70AB>AC20==V &545:AC.

5@54>7C20==O.

@8 28?04:>2>7C20==V &545:A<>7=0: B>:A8G=>ABV 2V47=0G5=> =5 1C>;
V:C20==O. =B84>BC F5DB81CB5=C =5 VA=CT, B>7C20==V <>6=0 ?@>25AB8 ?@><820==O H;C=:0.
=0G=0 :V;L:VABL &545:AC<>65 1CB8 2840;5=0 7 :@>2V 70 4>?><>3>N 35<>4V0;V7C. D5:B82=VABL
?5@8B>=50;L=>3> 4V0;V7C =5 2AB0=>2;5=0. # 74>@>28E 4>@>A;8E 4>1@>2>;LFV2, O:V >B@8
4=>@07>2> C 4>7V 4> 2 3, BO6:8E =51060=8E @50:FV9 =5 A?>AB5@V30;>AO, CAV :;V=VG=V V
;01>@0B>@=V ?>:07=8:8 70;8H0;8AL C <560E =>@<8.

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

45:20B=V :>=B@>;L>20=V 4>A;V465==O ?@5?0@0BC C 203VB=8E B0 ?V4 G0A ?>;>3V2 =5
?@>2>48;8AO, B>A>2C20B8 ?@5?0@0B ?@>B8?>:070=>. &5DB81CB5= ?@>=8:0T C 3@C4=5 <>;>:. #
=5<>2;OB ?@8 3>4C20==O 3@C44N <>6CBL A?>AB5@V30B8AO 7D;>@8 :8H5G=8:C 7 ?>O2>N

4V0@5W B0 :>=>V70FVW 4@V646>?>4V1=8<8 3@810<8; <>65 28=8:=CB8 =5>1EV4=VABL ?@8?8=8B8
3>4C20==O 3@C44N. >6;82VABL A5=A81V;V70FVW B0:>6 A;V4 27OB8 4> C2038# ?5@V>4
3>4C20==O 3@C44N ?@5?0@0B &545:A <>6=0 70AB>A>2C20B8 BV;L:8 B>4V, :>;8 >GV:C20=0
:>@8ABL 4;O <0B5@V ?5@528ICT ?>B5= FV9=89 @878: 4;O 48B8=8.

VB8.

57?5:0 B0 5D5:B82=VABL 70AB>AC20==O F5DB81CB5=C 4VBO< 4> 6 2;5=V, B>2V9 :0B53>@VW
?0FVT=BV2.

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

0FVT=B0< V7 =8@:>2>N =54>AB0B=VABN B0 ?0FVT=B0<, O:V ?5@51C20NBL =0 4V0;V7V,<>65 1CB8
=5>1EV4=0 77C20==O &545:AC (482. @>74V; «!>AV1 70AB>AC20==O B0 4>78»).

&545:A A;V4 >15@56=> ?@87=0G0B8 ?0FVT=B0< 7 0=0<=57>< CA::04=5=>3> H;C=:>2>-.8H:>2>3>
70E2>@N20==O, >A>1;82> E@>=VG=>3> :>;VBC.

?>A?>@8=>2V 0=B81V>B8:8 =5>1EV4=> ?@87=0G0B8 7 >15@56=VABN ?0FVT=B0< V7 2V4><>N 01>
?V4>7@N20=>N 0;5@3VTN =0 ?5=VF8;V=8. @81;87=> C 5 % E2>@8E V7 ?V4B25@465=>N 0;5@3VTN
=0 ?5=VF8;V= A?>AB5@V30TBLAO ?5@5E@5A=0 @50:B82=VABL =0 F5D0;>A?>@8=>2V
0=B81V>B8:8. # ?0FVT=BV2, O:V >B@84=>G0A=> ?5=VF8;V=8 V F5D0;>A?>@8=8, 1C;8
70@5TAB@>20=V A5@9>7=V 3>AB@V @50:FVW 3V?5@GCB;82>ABV =5309=>3> B8?C
(0=0DV;0:AVO); 2V4>6 28?04:8 ?5@5E@5A=>W 3V?5@50:B82=>ABV 7 @>728B:< 0=0DV;0:AVW. @8
28=8:=5==V BO6:8E 0;5@3VG=8E @50:FV9 =0 &545:A =5>1EV4=> ?@8?8=8B8 70AB>AC20==O
?@5?0@0BC V 268B8 2V4?>2V4=8E 70E>4V2. # 28?04:C 28=8:=5==O BO6:8E 0=0DV;0:B8G=8E @50:FV9
=5>1EV4=0 =52V4::04=0 B5@0?VO 70 =0O2=>ABV ;V=VG=8E ?>:070=L (04@5=0;V=,
2=CB@VH=L>25==5 22545==O @V48=8, 70157?5G5==O ?@>EV4=>ABV 48E0;L=8E H;OE2,
70157?5G5==O :8A=5<, 0=B83VAB0
@8 ;V:C20==V &545:A< B0 V=H8<8 0=B81V>B8:0<8 H8@>:>3> A?5:B@0 4VW ?>@CH5==O D;>@8
:8H5G=8:C <>65 ?@8725AB8 4> ?>O28 4V0@5W, A?@8G8=5=>W 70AB>AC20==O< 0=B81V>B8:V2,
2::NG0NG8 ?A524><5<1@0=>7=89 :>;VB, A?@8G8=5=89 B>:A8=< Clostridium difficile # ?0FVT=BV2
4V0@5O 2V4 A5@54=L>3> ABC?5=O BO6:>ABV 4> BO6:>3> 01> =02VBL 68BBT2> =5157?5G=>3> (7
453V4@0B0FVTN 01> 157) <>65 @>728=CB8AO O: ?V4 G0A, B0: V ?VA;O ;V:C20==O 28I52:070=8<8
0=B81V>B8:0<8. @> F59 4V03=>7 A;V4 ?0<OB0B8 2 CAVE 28?04:0E, :>;8 ABV9:0 4V0@5O 28=8:0T =0
B;V ?5@>@0;L=>3> 70AB>AC20==O &545:AC 01> V=H>3> 0=B81V>B8:0 H8@>:>3> A?5:B@0 4VW G8
G5@57 2 3> ?@89>
@07V ?>O28 AC4< 01> 0=0DV;0:B8G=>3> H>:C ?@8 ;V:C20==V &545:A< A;V4 =5309=> ?@8?8=8B8
;V:C20==O ?@5?0@0B< B0 >4@07C @>7?>G0B8 2V4?>2V4=C B5@0?VN.
A>1;82> >15@56=> A;V4 ?@87=0G0B8 &545:A ?0FVT=B0< 7 1C4L-O:8<8 0;5@3VG=8<8 @50:FVO<8
(=0?@8::04 0;5@3VG=89 :>=N=:B82VB 01> 1@>=EV0;L=0 0AB<0), >A:V;L:8 FV ?0FVT=B8 <>6CBL
<0B8 ?V428I5=89 @878: @>728B:C A5@9>7=8E @50:FV9 3V?5@GCB;82>ABV.
0?0E AV@:8<>65 2V4GC20B8AO ?@8 2V4:@8BBV ?0:5B8:V2: F5 =5 2V4>1@060TBLAO =0 O:>ABV
?@>4C:BC. VA;O @>7G8=5==O 70?0E 7=8:0T.
&545:A C D>@>@0;L=>W ACA?5=7VW A;V4 ?@89<0B8 =0BI5A5@F5.
&545:A C D>@>@0;L=>W ACA?5=7VW 7C. >3> =5 A;V4 70AB>A>2C20B8 E2>@8< V7 B0:8<8 @V4:VA=8
<8 A?04:>28<8 70E2>@N20==O<8 O: =5?5@5=>A878, A0E0@07=>-V7<0;LB07=0 =54>AB0B=VABL 01>
3;N:>7=>-30;0:B>7=0 <0;L01A>@1FVO.

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.

@5?0@0B =5 2?;820T =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.

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

A?5FV0;L=8E 4>A;V465==OE 282G0;0AO 270T<>4VO &545:AC 7 B0:8<8 ?@5?0@0B0<8 O: 0=B0F848,
I> :A84 0;N2V 01> D0@<0>:V=5B8:C B5>DV;V=C ?@8 ?@89>=52V4><89.

?>A?>@8=8, 2;:NG0NG8 F5DB81CB5=, 4C65 @V4:> <>6CBL 7=86C20B8 0:B82=VABL ?@>B@>1V=C, A?>@8G8=ONG8 ?>4>265==O ?@>B@><1V=>2>3> G0AC, >A>1;82> C ?0FVT=BV2, O:V @0=VH5 1C;8 AB01V;V7>20=V =0 B5@0?VW ?5@>@0;L=8<8 0=B8:>03C;O=B0<8. !;V4 @53C;O@=> :>=B@>;N20B8 ?@>B@><1V=>289 G0A 01> 4=89 =>@<0;V7>20=5 2V4=>H5==O () C ?0FVT=BV2 7 3@C?8 @878:C B0 70 =5>1EV4=>ABV 70AB>A>2C20B8 2VB0
> FL>3> G0AC =5 1C;> 70DV:A>20=> 6>4=8E 7=0GCI8E 270T<>4V9 7 V=H8<8 ?@5?0@0B0<8. ?;82 &545:AC =0 @57C;LB0B8 EV ;01>@0B>@=8E B5ABV2 =5 28O2;5=89. @8 70AB>AC20==V V=H8E F5D0;>A?>@8=V2 V=>4V @5TAB@C20;8 ?A524>?>78B82=C ?@01C C<1A0. 4=0: @57C;LB0B8 4>A;V465=L 7 28:>@8AB0==O 5@8B@>F8BV2 74>@>28E ;N459 4;O 287=0G5==O 740B=>ABV &545:AC 71C46C20B8 ?>78B82=C ?@>1C C<1A0 *in vitro*=5 28O28;8 ?>78B82=8E @50:FV9 =02VBL C :>=F5=B@0FVOE 4> 40 01A>@1FVN &545:C C D>@>@0;L=>W ACA?5=7VW.

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

\$0@<0:>48=0

&545:A T =0?V2A8=B5B8G=8< F5D0;>A?>@8=>28< 0=B81V>B8:> 10:B5@V9. V47=0G0;>AO, I> F5DB81CB5= T 28A>:>0:B82=8< (=87L:0) I>4> *E. coli*, *Klebsiella s@p.*, *Proteus*, *Salmonella spp.*, *Haemophilus influenzae* B0 *Streptococcus pyogenes* V= B0:>6 0:B82=89 2V4=>A=> *Citrobacter s@p.*, *Moraxella (Branhamella) catarrhalis*, *Morganella morganii* *Enterobacter s@p.*, *Serratia s@p.* B0 *Streptococcus pneumoniae*. 'CB;82V >@30=V7<8 2;:NG0NBL HB0<8 10:B5@V9, I> A?>@8G8=ONBL ?>O2C V=D5:FV9 25@E=VE B0 =86=VE 48E0;L=8E H;OEV2, 0 B0:>6 3>AB@8E B0 CA;:04=5=8E V=D5:FV9 A5G>282V4=8E H;OEV2. &5DB81CB5= =50:B82=89 I>4> AB0DV;>:>:V2, 5=B5@>:>:V2 01> *Pseudomonas s@p.*
=B810:B5@V0;L=0 4VO B0 <5E0=V7< 4VW. /: V 1V;LHVABL 15B0-;0:B0<=8E 0=B81V>B8:V2, 10:B5@V0;L=0 4VO F5DB81CB5=C 7C<>2;5=0 ?@83=VG5==O< A8=B57C 10:B5@V0;L=>W ABV=:8 >@30=V7W9 EV:>ABV9:8< 4> 4VW 15B0-;0:B0<07. V;LHVABL>@30=V7 ?@>4C:CNBL 15B0-;0:B0<078 V T ABV9:8<8 4> ?5=VF8;V=V2 01> V=H8E F5D0;>A?>@8=V2, <>6CBL ?@83=VGC20B8AO F5DB81CB5=>:>ABV9:8< 4> 4VW E@><>A><=8E F5D0;>A?>@8=07 B0 ?;07:@V< 15B0-;0:B0<07, I> ?@>4C:CNBLAO *Bacteroides fragilis* &5DB81CB5= 270T<>4VT 2 >A=>2=>□.A>IV, I> ?@872>48BL 4> CB2>@5==O DV;0<5=B>7=8E D>@< ?@8 :>=F5=B@0FVW, O:0 AB0=>28BL ¼½ IV ?@81;87=> 4>@V2=NT . 8A>:89 @V25=L 1V>4>ABC?=>ABV C ?>70;;VB8==V9 @V48=V 70157?5GCT 2?;82 F5DB81CB5=C =0 ?0B>35=8, O:V <0NBL ;8H5 ?>*in vitro*(482. @>74V; «\$0@ <0:>:V=5B8:0»).

=B810:B5@V0;L=0 4VO *in vitro*. &5DB81CB5= <0T 28@065=C 10:B5@8F84=C 4VN; ;V;L:VABL 6828E ::VB8= 10:B5@V9 @V7:> 7<5=HCTBLAO C :>=F5=B@0FVOE 50 % 01> 1V;LH5 70 ; C :>=F5=B@0FVOE, I> C 42VGV ?5@528ICNBL , 10:B5@8F84=0 4VO AB0=>28BL 99,9 % 7 2V4ACB=VABN ?>2B>@=>3> @>ABC 2?@>4>26 24 3>48=.

74>@>28E 4>1@>2>;LHV2, O:V >B@8&545:A C 4>7V 4> 2 3, BO6:8E =51060=8E @50:FV9 =5 A?>AB5@V30;>AL B0 2AV ;01>@0B>@=V ?>:07=8:8 ;8H0;8AL C<560E =>@<8.

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

@8 2=CB@VH=L>1@5 2A<>:BCTBLAO, 4>AO30NG8 <0:A8<0;L=>W :>=F5=B@0FVW C ?;072V G5@57 2-3 3>48=8. !5@54=O ?V:>20 :>=F5=B@0FVO C ?;072V ?VA;O >4=>@07>2>3> ?5@>@0;L=>3> ?@89>7V 200 <3 2V4?>2V40T 9,9 2V ?VA;O >4=>@07>2>3> ?5@>@0;L=>3> ?@89> F5DB81CB5=C C 4>7V 400 <3 AB0=>28;0 ?@81;87=> 17,0 @1FVO A;:040;0 ?@81;87=> 90 % 22545=>W 4>78, O:0 >FV=N20;0AO =0 ?V4AB02V 40=8E ?@> 282545==O 7 A5G5N.

5@>@0;L=89 ?@89>< &545:AC 2 :0?AC;0E C 4>7V 400 <3 7 28A>:>:0;>@V9=>N (800 :0;>@V9) 68@=>N W65N AC?@>2>46C202AO =525;8:8< 7=865==O< H284:>ABV, 0 =5 ABC?5=O 2A<>:BC20==O F5DB81CB5=C. # B>9 65 G0A ?@89>< ACA?5=7VW 7 28A>:>:0;>@V9=>N 68@=>N W65N A?>@8G8=O2 7 ABV B0 ABC?5=O 2A<>:BC20==O F5DB81CB5=C.

&5DB81CB5= ;53:> ?@8=8:0T 2 V=B5@AB8FV0;L=C @V48=C B0 4>AO30T :>=F5=B@0FV9, ?>4V1=8E 4> B8E, I> 2V47=0G0;8AO C A8@>20BFV :@>2V, 715@V30NG8 :>=F5=B@0FVN 2?@>4>26 B@820;>3> G0AC. A=>2=89 <5B01>;VB, F5DB81CB5=-B@0=A, O:89 <0T ?@81;87=> 2 8 @07V2 <5=HC 0=B81V>B8G=C 0:B82=VABL, 0=V6 F5DB81CB5=, AB0=>28BL 7,2-9,2 % 7030;L=>W :V;L:>ABV ?>2=VABN 282545=>3> ?@5?0@0BC. &5DB81CB5= 282>48BLAO =8@:0<8 B0 V7 A5G5N 5:A:@5BCTBLAO 62-68 % 2V4 22545=>W 4>78 C =57289 ;i@5=A ?@0:B8G=> V45=B8G=89 7030;L=> A2V4G8BL ?@> B5, I> F5DB81CB5= 284V;OTBLAO ?5@5206=> =8@:0<8. 5@V>4 =0?V2282545==O

F5DB81CB5=C C 74>@>28E ?0FVT=BV2 AB0=>28BL ?@81;87=> 2-2,3 3>48=8. # ?0FVT=BV2 7 ?>ABV, I> 2V4?>2V40T 65 % 4>78.

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

A=>2=V DV78:>-EVABV: ?>@>H>: 2V4 A2VB;>-6>2B>3> 4> B5<=>-6>2B>3> :>;L>@C, I> ?@8 @>7G8=5==V C 2>4V CB2>@NT A2VB;>-6>2BC ACA?5=7VN 7 E0@0:B5@=8< 28H=528< 70?0E>

"5@ABV. 2 @>:8.

#<>28 715@V30==O.

15@V30B8 ?@8 B5=5 28I5 25>! 2 =54>ABC?=>>B>2C ACA?5=7VN <>6=0 715@V30B8 ?@>BO3>< 14 4=V2 2 E>;>48;L=8:C (2- 8 °!).

#?0:>2:0.

>@>H>: C A::O=>=V 7 B5<=>3> A::0 7 ?;0AB8:>2>N :@8H:>N, I> 70328=GCTBLAO. > 1 D;0:>=C C :><, N ;>6:>N 01> 4>7CNG8< H?@8F>

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

8@>1=8:.

5@: (0@? V >C< >@?., !(/ Merck Sharp & Dohme Corp., USA.

VAF57=0E>465==O.

13900 >@B 5AB 57 >@B, 0O@840 33014, !(/ 13900 North West 57th Court, Miami Lakes, FL 33014, USA.