

!" #&/

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

>@07848<

(Lorazidime®)

!::04:

4VNG0 @5G>28=0: F5DB07848<;

1 D;0:>= 1000 <3;

4>?>28=8: =0B@VN :0@1>=0B 1572>4=89.

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

A=>2=V DV78:>-EVABV: :@8AB0;VG=89 ?>@>H>: 2V4 1V;>3> 4> :@5<>2>3> :>;L>@C.

\$0@<0:>B5@0?52B8G=0 3@C?0.

@>B81=V 70A>18 4;O A8AB5<=>3> 70AB>AC20==O. =HV β-;0:B0<=V 0=B81V>B8:8. ?>A?>@8=8 III
?>:>;V==O. &5DB07848

>4 "I J01D D02.

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

\$0@<0:>48=0

&5DB07848< F5 10:B5@8F84=89 F5D0;>A?>@8=>289 0=B81V>B8:, <5E0=V7< 4VW O:>3> ?>2O70=89 7
?>@CH5==O< A8=B57C ABV=>: 10:B5@V0;L=>W ;;VB8=8.

01CB0 @578AB5=B=VABL 4> 0=B81V>B8:02V4@V7=OTBLAO C @V7=8E @53V>=0E B0 <>65 7<, 0
4;O >:@5<8E HB00 ACBBT2>. 060=> 28:>@8AB>2C20B8 :0;L=V) 40=V I>4> GCB;82>ABV 4>
0=B81V>B8:0, >A>1;82> ?@8 ;V:C20==V BO6:8E V=D5:FV9.

'CB:82V >@30=V7<8

@078B82=V 05@>18: *Streptococcus pyogenes, Streptococcus agalactiae.*

@0<=530B82=V 05@>18: *Citrobacter koseri, Escherichia coli, Haemophilus influenza, Moraxella catarrhalis, Neisseria meningitides, Proteus mirabilis, Proteus spp., Providencia spp.*

(B0<8 7 <>6;82>N =01CB>N @578AB5=B=VABN

@0<=530B82=V 05@>18: *Acinetobacter baumannii*, *Burkholderia cepacia*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *Serratia spp.*, *Morganella morgani*.

@078B82=V 05@>18: *Staphylococcus aureus*, *Staphylococcus pneumonia*.

@078B82=V 0=05@>18: *Clostridium perfringens*, *Peptococcus spp.*, *Peptostreptococcus spp.*,

@0<=530B82=V 0=05@>18: *Fusobacterium spp.*

5GCB;82V >@30=V7<8

@078B82=V 05@>18: *Enterococcus spp.*, 2;NG0NG8 *E. faecalis* B0 *E. faecium*, *Listeria spp.*.

@078B82=V 0=05@>18: *Clostridium difficile*

@0<=530B82=V 0=05@>18: *Bacteroides spp.*, 2;NG0NG8 *B. fragilis*

=HV: *Chlamydia spp.*, *Mycoplasma spp.*, *Legionella spp.*.

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

?0FVT=BV2 ?VA;O 2=CB@VH=L<O7>2>W V=T:FVW 500<3 B0 1 3 H284:> 4>AO30NBLAO A5@54=V ?V:>2V :=F5=B@0FVW 18 V 37<3/; 2V4?>2V4=>. '5@57 5 E28;8= ?VA;O 2=CB@VH=L>25==>3> 1>;NA=>3> 22545==O 500 <3, 1 3 01> 2 3 C A8@>20BFV :@>2V 4>AO30NBLAO :=F5=B@0FVW C A5@54=L> 170 <3/; 2V4?>2V4=>. "5@0?52B8G=> 5D5:B82=V :=F5=B@0FVW 70;8H0NBLAO C A8@>20BFV :@>2V =02VBL G5@57 8-12 3>48= ?VA;O 2=CB@VH=L>25==>3> B0 2=CB@VH=L> <O7>2>3> 22545==O. 2O7C20==O 7 1V;:0<8 ?;07<8 :@>2V AB0=>28BL ?@81;87=> 10 %. :=F5=B@0FVO F5DB07848 ?5@528ICT 4;O 1V;LH>ABV @>7?>2AN465=8E ?0B>35==8E>@30=V7AO30TBLAO C B0:8E B:0=8=0E V A5@54>28I0E O: :VAB:8, A5@F5, 6>2G,<:@>B8==O, 2=CB@VH=L>>G=0, A8=>2V0;L=0, ?;52@0;L=0 B0 ?5@8B>=50;L=0 @V48=8. &5DB07848< H284:> ?@>=8:0T :@V7L ?;0F5=BC B0 C 3@C4=5 <>;>: . @5?0@0B ?>30=> ?@>=8:0T :@V7L =5CH:>465=89 35<0B>5=F5D0;VG=89 10@ T@, ?@8 2V4ACB=>ABV 70?0;5==O :=F5=B@0FVO ?@5?0@0BC C &! =525;8:0. 4=0: ?@8 70?0;5==V <>7:>28E >1>;>=: :=F5=B@0FVO F5DB0784828BL 4-20 <3/; V 28I5, I> 2V4?>2V40T @V2=N 9>3> B5@0?52B8G=>W :=F5=B@0FVW.

&5DB07848< =5 <5B01>;V7CTBLAO 2 >@30=V73> 22545==O 4>AO30TBLAO 28A>:0 B0 ABV9:0 :=F5=B@0FVO F5DB0784820BFV :@>2V. 5@V>4 =0?V2282545==O AB0=>28BL ?@81;87=> 2 3>48=8. @5?0@0B 282>48BLAO C =57@< 3;><5@C;O@=>W DV;LB@0FVW; ?@81;87=> 80-90 % 4>78 282>48BLAO V7 A5G5N ?@>BO3< 24 3>48=. # ?0FVT=BV2 V7 ?>@CH5==O< DC=:FVW =8@>: 5;V7C A;V4 7<5=HC20B8. 5=H5 1 % ?@5?0@0BC 282>48BLAO 7 6>2GN, I> 7=0G=> >1<56CT :V;L:VABL ?@5?0@0BC, O:0 ?>B@0?;OT C :8H5G=8:.

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

>:070==O.

V:C20==O =02545=8E =86G5 V=D5:FV9 C 4>@>A;8E B0 4VB59, 2;NG0NG8 =>2>=0@>465=8E:

- 2=CB@VH=L>;V:0@=O=0 ?=52<>=VO;

- V=D5:FVW 48E0;L=8E H;OEV2 C E2>@8E =0 2VAF84>7;

- 10:B5@V0;L=89 <5=V=3VB;

- E@>=VG=89 A5@54=V9 >B8B;

- 7;>O:VA=89 7>2=VH=V9 >B8B;
- CA::04=5=V V=D5:FVW A5G>282V4=8E H;OEV2;
- CA::04=5=V V=D5:FVW H:V@8 B0 <O:8E B:0=8=;
- CA::04=5=V V=D5:FVW G5@52=>W ?>@>6=8=8;
- V=D5:FVW :VAB>: V AC3;>1V2;
- ?5@8B>=VB, ?>2O70=89 7 ?@>2545==O< 4V0;V7C C E2>@8E, O:V 7=0E>4OBLAO =0
157?5@5@2=>=50;L=>

V:C20==O 10:B5@VT 28=8:0T C ?0FVT=BV2 C @57C;LB0BV 1C4L-O:>W 7 =02545=8E 28I5 V=D5:FV9.

&5DB07848< <>6=0 70AB>A>2C20B8 4;O ;V:C20==O E2>@8E V7 =59B@>?5=VTN B0 30@OG:>N, I>
28=8:0T C @57C;LB0BV 10:B5@V0;L=>W V=D5:FVW.

&5DB07848< <>6=0 70AB>A>2C20B8 4;O ?@>DV;0:B8:8 V=D5:FV9=8E CA::04=5=L ?@8 >?5@0FVOE
=0 ?5@542V9 70;>7V (B@0=AC@5B@0;L=0 @575:FVO).

@8 ?@87=0G5==V F5DB078482C20B8 9>3> 0=B810:B5@V;L=89 A?5:B@, A:5@>20=89 3>;>2=8< G8=><
?@>B8 3@0<=530B82=8E 05@>1V2 (482. @>74V;8 «A>1;82>ABV 70AB>AC20==O» B0 «\$0@
<0.>;>3VG=V 2;0AB82>ABV»).

&5DB07848< A;V4 70AB>A>2C20B8 7 V=H8<8 0=B810:B5@V0;L=8<8 70A>10<8, O:I> >GV:CTBLAO, I>
@O4 >@30=V7 A?@8G8=8;8 V=D5:FVN, =5 ?V4?040NBL ?V4 A?5:B@ 4VW F5DB07848

@87=0G0B8 ?@5?0@0B A;V4 73V4=> 7 VA=CNG8<8 >DV9=8<8 @5:><5=40FVO<8 I>4>
?@87=0G5==O 0=B810:B5@V0;L=8E 70A>1V2.

@>B8?>:070==O. V428I5=0 GCB;82VABL 4> F5DB078484> V=H8E :>=5=BV2 ?@5?0@0BC.

V428I5=0 GCB;82VABL 4> F5D0;>A?>@8=>28E 0=B81V>B8:V2.

0O2=VABL 2 0=0<=57V BO6:>W 3V?5@GCB;82>ABV (=0?@8::04, 0=0DV;0:B8G=V @50:FVW) 4> V=H8E

β;:0:B0<=8E 0=B81V>B8:V2 (?5=VF8;V=8, <>=>10:B0<8 B0 :0@10?5=5<8).

70T<>4V0 7 V=H8<8 ;V:0@AL:8<8 70A>10<8 B0 V=HV 2848 270T<>4V9.

4=>G0A=5 70AB>AC20==O 28A>:8E 4>7 ?@5?0@0BC 7 =5D@>B>:A8G=8<8 ;V:0@AL:8<8 70A>10<8
<>65 =530B82=> 2?;820B8 =0 DC=:FVN =8@>: (482. @>74V; «A>1;82>ABV 70AB>AC20==O»).

%;>@0; in vitro T 0=B03>=VAB< F5DB07848A?>@8=V2. ;V=VG=5 7=0G5==O FL>3> O28I0 =52V4><5,
?@>B5, O:I> ?@>?>=CTBLAO >4=>G0A=5 70AB>AC20==O >@07848@0;><, A;V4 2@0E>2C20B8
<>6;82VABL 0=B03>=V7

/: V V=HV 0=B81V>B8:8, >@07848< <>65 2?;820B8 =0 D;>@C :8H5G=8:C, I> ?@872>48BL 4> 7
<5=H5==O @501A>@1FVW 5AB@>35=V2 B0 7=865==O 5D5:B82=>ABV :><1V=>20=8E ?5@>@0;L=8E
:=B@0F5?B82=8E 70A>1V2.

&5DB07848< =5 2?;820T =0 @57C;LB0B8 287=0G5==O 3;N:>7C@VW 5=78<=8<8 <5B>40<8, ?@>B5 =525;8:89 2?;82 =0 @57C;LB0B8 0=0;V7C <>65 A?>AB5@V30B8AO ?@8 70AB>AC20==V <5B>4V2 2V4=>2;5==O

&5DB07848< =5 2?;820T =0 ;C6=>?V:@0B=89<5B>4 287=0G5==O :@50B8=V=C.

A>1;82>ABV 70AB>AC20==O. /: V ?@8 70AB>AC20==V V=H8E β-;0:B0<=8E 0=B81V>B8:V2, ?>2V4< <;O;>AO ?@> BO6:V B0 G0A<< ;5B0;L=V @50:FVW 3V?5@GCB;82>ABV. # @07V 28=8:=5==O BO6:8E @50:FV9 3V?5@GCB;82>ABV ;V:C20==O F5DB07848<<< A;V4 =5309=> ?@8?8=8B8 B0 @>7?>G0B8 2V4?>2V4=V =52V4.;04=V 70E>48.

5@54 ?>G0B:>< ;V:C20==O A;V4 287=0G8B8 C ?0FVT=B0 =0O2=VABL 2 0=0<=57V BO6:8E @50:FV9 3V?5@GCB;82>ABV 4> F5DB07848A?>@8=>28E 0=B81V>B8:V2 01> V=H8E β-;0:B0<=8E 0=B81V>B8:V2. >15@56=VABN ?@5?0@0B ?@87=0G0B8 ?0FVT=B0<, C O:8E 1C;8 =5A5@9>7=V @50:FVW 3V?5@GCB;82>ABV =0 V=HV β ;0:B0<=V 0=B81V>B8:8.

&5DB07848< <0T >1<565=89 A?5:B@ 0=B810:B5@V;L=>W 0:B82=>ABV. V= =5 T ?@89=OB=8< ?@5?0@0B<< 4;O <>=>B5@?VW 45O:8E B8?V2 V=D5:FV9, O:I> BV;L:8 =52V4<<89 71C4=8: E2>@>18 V =52V4<<<, I> 2V= T GCB;828< 4> FL>3> ?@5?0@0BC 01> VA=CT 25;8:0 2V@>3V4=VABL B>3>, I> <>6;8289 71C4=8: 1C45 GCB;828< 4> ;V:C20==O F5DB07848<>A>1;82> 206;82>, :>8 28@VHCTBLAO ?8B0==O ?@> ;V:C20==O ?0FVT=BV2 7 10:B5@VTβ-;0:B0<070<8 7 @>7H8@5=8< A?5:B@<< 4VW. "> @V F5DB078482C20B8 V=D>@<0FVN ?@> @>7?>2AN465==O >@30=V7 ?@>4C:CNBL β-;0:B0<078 7 @>7H8@5=8< A?5:B@<< 4VW.

4=>G0A=5 ;V:C20==O 28A>:8<8 4>70<8 F5D0;>A?>@8=V2 V =5D@>B>:A8G=8<8 ?@5?0@0B0<8, B0:8 <8 O: 03;V:>7848 01> A8;L=>4VNGV 4VC@5B8:8 (=0?@8.;04, DC@>A5:0702, I> ?@8 4>B@8<0==V @5:> <5=4>20=>3> 4>7C20==O F5 O28I5 <0;>9<>2V@=5. 5<0T 40=8E, I> F5DB07848< =5A?@8OB;82> 2?;820T =0 DC=:FVN =8@>: C 728G09=8E B5@0?52B8G=8E 4>70E.

&5DB07848< 282>48BLAO =8@:0<8, B>7C A;V4 7<5=HC20B8 2V4?>2V4=> 4> ABC?5=O C@065==O =8@>.: >2V4<<<;O;>AO ?@> 28?04:8 =52@>;>3VG=8E CA.;04=5=L, :>8 4>70 =5 1C;0 2V4?>2V4=> 7 <5=H5=0 (482. @>74V;8 «!>AVI 70AB>AC20==O B0 4>78» B0 «>1VG=V @50:FVW»).

/: V ?@8 70AB>AC20==V V=H8E 0=B81V>B8:V2 H8@>:>3> A?5:B@0 4VW, B@820;5 ;V:C20==O >@07848<<< <>65 ?@8725AB8 4> =043> @>ABC =5GCB;828E >@30=V7Candida, Enterococci); C FL>

@8 70AB>AC20==V 0=B81V>B8:V2 ?>2V4<<<;O;>AO ?@> 28?04:8 ?A524<<5<1@0=>7=>3> :>;VBC, I> <>65 1CB8 @V7=>3> ABC?5=O BO6:>ABV 2V4 ;53:>3> 4> B0:>3>, I> 703@>6CT 68BBN. "> 72068B8 =0 2AB0=>2;5==O FL>3> 4V03=>7C C ?0FVT=BV2, C O:8E 28=8.;0 4V0@50 ?V4 G0A 01> ?VA;O 70AB>AC20==O 0=B81V>B8:0. # @07V B@820;>W B0 7=0G=>W 4V0@5W 01> O:I> C ?0FVT=B0 28=8:0NBL 014>Clostridium difficile 5 A;V4 ?@87=0G0B8 ;V:0@AL:V 70A>18, I> C?>2V;L=NNBL ?5@8AB0;LB8:C :8H5G=8:C.

/: V ?@8 70AB>AC20==V V=H8E F5D0;>A?>@8=V2 V ?5=VF8;V=V2 H8@>:>3> A?5:B@0 4VW, 45O:V @0=VH5 GCB;82V HB0<8 Enterobacter spp. V Serratia spp. <>6CBL AB0B8 @578AB5=B=8<8 ?V4 G0A ;V:C20==O F5DB07848<>48G=> 28:>=C20B8 4>A;V465==O =0 GCB;82VABL.

>@07848< C A2>T= 7 500 <3 F5DB078481 3 F5DB07848

0AB>AC20==O C ?5@V>4 203VB=>ABV 01> 3>4C20==O 3@C44N. 0=V I>4> ;V:C20==O F5DB07848<><
 203VB=8E >1<565=V. >A;V465==O =0 B20@8=0E =5 2:07CNBL =0 ?@O<89 01> =5?@O<89 H:V4;8289
 2?;82 =0 203VB=VABL, 5<1@V>=0;L=89 01> ?>AB=0B0;L=89 @>728B>:. @87=0G0B8 ?@5?0@0B
 203VB=8< A;V4 BV;L:8 B>4V, :>;8 :>@8ABL 2V4 9>3> 70AB>AC20==O ?5@52060T<>6;8289 @878:.

&5DB07848< 5:A:@5BCTBLAO C 3@C4=5 <>;> C =525;8:8E :V;L:>ABOE, 0;5 ?@8 70AB>AC20==V
 B5@0?52B8G=8E 4>7 2?;82C =0 =5<>2;O, O:5 7=0E>48BLAO =0 3@C4=>4C20==V, =5 >GV:CTBLAO.
 &5DB07848< <>6=0 70AB>A>2C20B8 C ?5@V>4 3>4C20==O 3@C44N.

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.

V4?>2V4=8E 4>A;V465=L =5 ?@>2>48;>AO. ;5 28=8:=5==O B0:8E ?>1VG=8E @50:FV9 O: 70?0
 <>@>G5==O <>65 2?;8=CB8 =0 740B=VABL :5@C20B8 02B>B@0=A?>@B< 01> V=H8<8 <5E0=V7<0<8
 (482. @>74V; <>1VG=V @50:FVW»).

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

>@>A;V B0 4VB8 ≥ 40 :3

=B5@	
=D5:FVO	>70, I> 22>48BLAO
V=D5:FVW 48E0;L=8E H;OEV2 C E2>@8E =0 2VAF84>7	100-150 <3/:3 <0A8 BV;0/=0 4>1C :>6=V 8 3>48=, <0:A8<0;L=> 4> 9 3 =0 4>1C1
D51@8;L=0 =59B@>?5=VO	2 3 :>6=V 8 3>48=
2=CB@VH=L>;V:0@=O=0 ?=52<>=VO	
10:B5@V0;L=89 <5=V=3VB	
10:B5@VT	
V=D5:FVW :VAB>: V AC3;>1V2	1-2 3 :>6=V 8 3>48=
CA:;04=5=V V=D5:FVW H:V@8 B0 <O:8E B:0=8=	
CA:;04=5=V V=B@0014>	
?5@8B>=VB, ?>2O70=89 7 157?5@5@2=8 < 0<1C;0B>@=8< ?5@8B>=50;L=8< 4V0;V7><<	
CA:;04=5=V V=D5:FVW A5G>282V4=8E H;OEV2	1-2 3 :>6=V 8 3>48= 01> 12 3>48=
?@>DV;0:B8:8 V=D5:FV9=8E CA:;04=5=L ?@8 >?5@0FVOE =0 ?5@542V9 70;>7V (B@0=AC@5B@0;L=0 @575:FVO)	1 3 ?V4 G0A V=4C:FVW 2 0=5AB57VN, 1 3 C <><5=B 2840;5==O :0B5B5@0
E@>=VG=89 A5@54=V9 >B8B	1-2 3 :>6=V 8 3>48=
7;>O:VA=89 7>2=VH=V9 >B8B	
>ABV9=0 V=DC7VO	
=D5:FVO	>70, I> 22>48BLAO
D51@8;L=0 =59B@>?5=VO	
2=CB@VH=L>;V:0@=O=0 ?=52<>=VO	

V=D5:FVW 48E0;L=8E H;OEV2 C E2>@8E	2>48BLAO =020=B06C20;L=0 4>70 2 3 7 =0ABC?=8< ?>ABV9=8< V=DC7V9=8< 22545==O< 2V4 4 4> 6 3 :>6=V 24 3>48=81
=0 2VAF84>7	
10:B5@V0;L=89 <5=V=3VB	
10:B5@VT	
V=D5:FVW :VAB>: V AC3;>1V2	
CA::04=5=V V=D5:FVW H:V@8 B0 <O:8E B:0=8=	
CA::04=5=V V=B@0014>	
?5@8B>=VB, ?>2O70=89 7 157?5@5@2=8 < 0<1C;0B>@=8< ?5@8B>=50;L=8< 4V0;V7><	
1 # 4>@>A;8E ?0FVT=BV2 V7 =>@<0;L=>N DC=:FVTN =8@>: 9 3 =0 4>1C 70AB>A>2C20;>AO 157 ?>1VG=8E @50:FV9.	

VB8 < 40 :3

5<>2;OB0 B0 4VB8 2V:>> 2 < 40 :3	=D5:FVO	28G09=0 4>70
=B5@		
	CA::04=5=V V=D5:FVW A5G>282V4=8E H;OEV2 E@>=VG=89 A5@54=V9 >B8B	100-150 <3/:3 <0A8 BV;0/=0 4>1C C 3 ?@89><8, <0:A8<0;L=> 6 3 =0 4>1C
	7;>O:VA=89 7>2=VH=V9 >B8B	
	=59B@>?5=VO C 4VB59	
	V=D5:FVW 48E0;L=8E H;OEV2 C E2>@8E =0 2VAF84>7	150 <3/:3 <0A8 BV;0/=0 4>1C C 3 ?@89><8, <0:A8<0;L=> 6 3 =0 4>1C
	10:B5@V0;L=89 <5=V=3VB	
	10:B5@VT	
	V=D5:FVW :VAB>: V AC3;>1V2	
	CA::04=5=V V=D5:FVW H:V@8 B0 <O:8E B:0=8=	
	CA::04=5=V V=B@0014>	100-150 <3/:3 <0A8 BV;0/=0 4>1C C 3 ?@89><8, <0:A8<0;L=> 6 3 =0 4>1C
	?5@8B>=VB, ?>2O70=89 7 157?5@5@2=8< 0 <1C;0B>@=8< ?5@8B>=50;L=8< 4V0;V7> <	
	>ABV9=0 V=DC7VO	
	D51@8;L=0 =59B@>?5=VO	
	2=CB@VH=L>;V:0@=O=0 ?=52<>=VO	
	V=D5:FVW 48E0;L=8E H;OEV2 C E2>@8E =0 2VAF84>7	
	10:B5@V0;L=89 <5=V=3VB	

	10:B5@VT	
	V=D5:FVW :VAB>: V AC3;>1V2	2>48BLAO =020=B06C20;L=0 4>70 60-100 <3/:3 <0A8 BV;0 7 =0ABC?=8< ?>ABV9=8< V=DC7V9=8< 22545==O<
	CA:;04=5=V V=D5:FVW H:V@8 B0 <O:8E B:0=8=	100-200 <3/:3 <0A8 BV;0 =0 4>1C, <0:A8<0;L=> 4> 6 3 =0 4>1C
	CA:;04=5=V V=B@0014>	
	?5@8B>=VB, ?>2O70=89 7 157?5@5@2=8< 0 <1C;0B>@=8< ?5@8B>=50;L=8< 4V0;V7> <	
5<>2;OB0 B0 4VB8 2V:>≤ 2	=D5:FVO	28G09=0 4>70
=B5@		
	V;LHVABL V=D5:FV9	25-60 <3/:3 <0A8 BV;0/4>1C C 2 ?@89><81
1# =5<>2;OB B0 4VB59 2V:>≤ 2 4 =02V2282545==O V7 A8@>20B:8 :@>2V <>65 1CB8 C 2-3 @078 1V;LH89 =V6 C 4>@>A;8E		

*O:I> F5 0A>FVNTBLAO 01> T ?V4>7@0 =0 0A>FVN20==O 7 V=D5:FVO<8, =02545=8<8 C @>74V;V
<<:070==O».

VB8

57?5:0 B0 5D5:B82=VABL 70AB>AC20==O >@07848< ?>ABV9=>W 2@CB@VH=L>25==>W V=DC7VW
C =5<>2;OB B0 4VB59 ≤ 2 2;5=V.

0FVT=B8 ;VB=L>3> 2V:C

@0E>2CNG8 7=865==O ::V@5=AC F5DB07848@8E ;VB=L>3> 2V:C, O:V <0NBL 3>AB@V V=D5:FVW,
4>1>20 4>70 70728G09 =5 ?>28==0 ?5@528IC20B8 3 3, >A>1;82> C ?0FVT=BV2 2V:>≤ 2V4 80 @>:V2.

5GV=:>20 =54>AB0B=VABL

5>1EV4=>ABV C 77C20==O 4;O E2>@8E V7 ;53:>N B0 ?>N ?5GV=:>2>N =54>AB0B=VABN =5<0T.
;V=VG=8E 4>A;V465=L C E2>@8E V7 BO6:>N ?5GV=:>2>N =54>AB0B=VABN =5 ?@>2>48;>AO. 5:>
<5=4CTBLAO @5B5;L=89 ::V=VG=89 =03;O4 70 5D5:B82=VABN B0 157?5:>N 70AB>AC20==O.

8@:>20 =54>AB0B=VABL

&5DB07848< 282>48BLAO =8@:0<8 C =57

>G0B:>20 4>70 ?>28==0 AB0=>28B8 1 3. 87=0G5==O ?V4B@8W 4>78 ?>28==> 107C20B8AO =0
H284:>ABV 3;>≤5@C;O@=>W DV;LB@0FVW.

5:><5=4>20=V ?V4B@878 F5DB078482V9 =54>AB0B=>ABV V=B5@

$\geq @ > A; V B_0 4VB_8 \geq 40 :3 < 0A_8 BV;0$

;V@5=A :@50B8=V=C, < ;/E2	@81;87=89 @V25=L :@50B8=V=C C A8@>20BFV :@>2V,	5:><5=4>20=0 >4=>@07>20 4>70 F5DB07848	'0AB>B0 4>7C20==O (3>4)
50-31	150-200 (1,7-2,3)	1	12
30-16	200-350 (2,3-4)	1	24
15-6	350-500 (4-5,6)	0,5	24
< 5	> 500 (> 5,6)	0,5	48

0FVT=B0< V7 B06:8<8 V=D5:FVO<8 >4=>@07>2C 4>7C <>6=0 71V;LH8B8 =0 50 % 01> 2V4?>2V4=> 71V;LH8B8 G0AB>BC 22545==O. "0:8< ?0FVT=B0< @5:><5=4CTBLAO :=>B@>;N20B8 @V25=L F5DB0784820BFV :@>2V.

4VB59 ;:V@5=A :@50B8=V=C A;V4 2V4:>@83C20B8 2V4?>2V4=> 4> ?;>IV ?>25@E=V BV;0 01> 4> <0A8 BV;0.

$VB_8 \leq 40 :3$

;V@5=A :@50B8=V=C, < ;/ E2**	@81;87=89 @V25=L :@50B8=V=C* C A8@>20BFV :@>2V,	5:><5=4>20=0 V=482V4C0;L=0 4>70 <3/:3 <0A8 BV;0	'0AB>B0 4>7C20==O (3>4)
50-31	150-200 (1,7-2,3)	25	12
30-16	200-350 (2,3-4)	25	24
15-6	350-500 (4-5,6)	12,5	24
< 5	> 500 (> 5,6)	12,5	48

*F5 @V25=L :@50B8=V=C C A8@>20BFV :@>2V, @>7@0E>20=89 2V4?>2V4=> 4> @5:><5=40FV9, V <>65 B>G=> =5 2V4?>2V40B8 @V2=N 7<5=H5==O DC=:FVW =8@>: C 2AVE ?0FVT=BV2 7 =8@>:2>N =54>AB0B=VABN.

** ;:V@5=A :@50B8=V=C, 28@0E>20=89 =0 >A=>2V ?;>IV ?>25@E=V BV;0, 01> 287=0G5=89.

5:><5=4CTBLAO @5B5;L=89 ;:V=VG=89 =03;04 70 5D5:B82=VABN B0 157?5:>N 70AB>AC20==O.

5: > < 5 = 4 > 20 = V ? V4B@878 F5DB078482V9 = 54 > AB0B => ABV ? > ABV9 = 0 V = DC7VO

> @ > A; V B0 4VB8 > 40 :3 < 0A8 BV; 0

;V@5=A :@50B8=V=C, < ;/E2	@81;87=89 @V25=L :@50B8=V=C C A8@>20BFV :@>2V,	'0AB>B0 4>7C20==O (3>4)
50-31	150-200 (1,7-2,3)	2>48BLAO =020=B06C20;L=0 4>70 2 3 7 =0ABC?=8< ?>ABV9=8< V=DC7V9=8< 22545==O< 2V4 1 4> 3 3 :>6=V 24 3>48=8
30-16	200-350 (2,3-4)	2>48BLAO =020=B06C20;L=0 4>70 2 3 7 =0ABC?=8< ?>ABV9=8< V=DC7V9=8< 22545==O< 1 3 :>6=V 24 3>48=8
≤ 15	> 350 (4-5,6)	5 4>A;V46C20;>AO

81V@ 4>78 A;V4 ?@>2>48B8 7 >15@56=VABN. 5: < 5 = 4CTBLAO @5B5;L=89 ;V=VG=89 =03;O4 70
5D5:B82=VABN B0 157?5:>N 70AB>AC20==O.

VB8 ≤ 40 :3

57?5:0 B0 5D5:B82=VABL 70AB>AC20==O >@07848< ?>ABV9=>W 2@CB@VH=L>25==>W V=DC7VW
4VBO<, <0A0 BV;0 O:8E < 40 :3, V7 ?>@CH5=>N DC=:FVTN =8@>: =5 2AB0=>2;5=V. 5: < 5 = 4CTBLAO
@5B5;L=89 ;V=VG=89 =03;O4 70 5D5:B82=VABN B0 157?5:>N 70AB>AC20==O.

/:I> 4VBO< V7 ?>@CH5=>N DC=:FVTN =8@>: =5>1EV4=> 70AB>AC20B8 ?@5?0@0B H;OE<<
>ABV9=>W 2=CB@VH=L>25==>W V=DC7VW, A;V4 ;V@5=A :@50B8=V=C A :>@53C20B8
2V4?>2V4=> 4> ?;>IV ?>25@E=V BV;0 48B8=8 01> <0A8 BV;0.

5 < 4V0;V7

5@V>4 =0?V2282545==O F5DB0784820B:8 :@>2V ?V4 G0A 35<>4V0;V7C AB0=>28BL 2V4

3 4> 5 3>48=.

VA;O :>6=>3> A50=AC 35<>4V0;V7C A;V4 22>48B8 ?V4B@87C F5DB07848 @5: < 5 = 4CTBLAO C
B01;8FV, =02545=V9 =86G5.

5@8B>=50;L=89 4V0;V7

&5DB07848< <>6=0 70AB>A>2C20B8 ?@8 ?5@8B>=50;L=>=50;L=>

@V< 2=CB@VH=L>25==>3> 70AB>AC20==O, F5DB07848< <>6=0 2;;NG0B8 4> 4V0;V7=>W @V48=8
(70728G09 2V4 125 4> 250 <3 =0 2 ; 4V0;V7=>3> @>7G8=C).

;O ?0FVT=V2 V7 =8@>2>N =54>AB0B=VABN, O:8< ?@>2>48BLAO B@820;89 0@B5@V>25=>7=89 35
<>4V0;V7 01> 28A>:>?>B>G=0 35<>DV;LB@0FVVO C 2V44V;5==OE V=B5=A82=>W B5@0?VW, @5:>
<5=4>20=0 4>70 AB0=>28BL 1 3 =0 4>1C C 283;O4V >4=>@07>2>W 4>78 01> 70 :V;L:0 ?@89>
>?>B>G=>W 35<>DV;LB@0FVW A;V4 70AB>A>2C20B8 4>78, O: ?@8 ?>@CH5==V DC=:FVW =8@>:.

0FVT=B0<, O:8< ?@>2>48BLAO 25=>25=>7=0 35<>DV;LB@0FVO B0 25=>25=>7=89 35<>4V0;V7, @5:><5=40FVW 7 4>7C20==O =02545=V C B01;8FOE.

5:><5=40FVW 7 4>7C20==O F5DB07848

5784C0;L=0 DC=:FVO =8@>: (:;V@5=A :@50B8=V=C, <:/E2)	V4B@870 (<3) 70;56=> 2V4 H284:>ABV C;LB@0DV;LB@0FVW (<:/E2) ⁰			
	5	16,7	33,3	50
0	250	250	500	500
5	250	250	500	500
10	250	500	500	750
15	250	500	500	750
20	500	500	500	750

0V4B@87C A;V4 22>48B8 :>6=V 12 3>48=.

5:><5=40FVW 7 4>7C20==O F5DB07848

5784C0;L=0 DC=:FVO =8@>: (:;V@5=A :@50B8=V=C, <:/E2)	V4B@870 (<3) 4;O 4V0;V70BC ?@8 H284:>ABV ?>B>:C (<:/E2) ⁰					
	1 ;/3>4			2 ;/3>4		
	(284:VABL C;LB@0DV;LB@0FVW (;/3>4)			(284:VABL C;LB@0DV;LB@0FVW (;/3>4)		
	0,5	1	2	0,5	1	2
0	500	500	500	500	500	750
5	500	500	750	500	500	750
10	500	500	750	500	750	1000
15	500	750	750	750	750	1000
20	750	750	1000	750	750	1000

0V4B@87C A;V4 22>48B8 :>6=V 12 3>48=.

2545==O.

>@07848< 22>48B8 2=CB@VH=L>25==> V=T:FV9=> 01> V=DC7V9=> 01> H;OE<< 3;81>:>W
2=CB@VH=L<<O7>2>W V=T:FVW. 5:<5=4>20=8<8 4V;O=:0<8 4;O 2=CB@VH=L<< O7>2>3>
22545==O T 25@E=V9 7>2=VH=V9 :204@0=B 25;8:>3> AV4=8G=>3>< O70 01> ;0B5@0;L=0 G0AB8=0
AB53=0.

>7G8=8 F5DB0784825==8E V=DC7V9, O:I> ?0FVT=B >B@8.

>70 70;568BL 2V4 BO6:>ABV 70E2>@N20==O, GCB;82>ABV, ;>:0;V70FVW B0 B8?C V=D5:FVW, 0
B0:>6 2V4 2V:C B0 DC=:FVW =8@>: ?0FVT=B0.

01CB0 @578AB5=B=VABL 4> 0=B81V>B8:02V4@V7=OTBLAO C @V7=8E @53V>=0E B0 <>65 7<, 0
4;O >:@5<8E HB028:>@8AB>2C20B8 :0;L=V) 40=V I>4> GCB;82>ABV 4> 0=B81V>B8:0, >A>1;82> ?@8
;V:C20==V BO6:8E V=D5:FV9.

=AB@C:FVO 7 ?@83>BC20==O

>@07848< AC:>26820=8E @>7G8=V2 4;O 2=CB@VH=L>25==>3> 22545==O. 4=0: =5 A;V4
70AB>A>2C20B8 O: @>7G8==8: =0B@VN 1V:0@1>=0B 4;O V= T:FV9

(482. «5AC).

>70, I> 22>48BLAO		5>1EV4=0 :V;L:VABL @>7G8==8:0 (<);	@81;87=0 :=F5=B@0FVO (<3/ <);
250 <3	=CB@VH=L>< O7>2> =CB@VH=L>25==89 1>;NA	1 2,5	210 90
500 <3	=CB@VH=L>< O7>2> =CB@VH=L>25==89 1>;NA	1,5 5	260 90
1 3	=CB@VH=L>< O7>2> =CB@VH=L>25==89 1>;NA =CB@VH=L>25==0 V=DC7VO	3 10 50*	260 90 20

*@8 >7G8=5==O A;V4 ?@>2>48B8 C 420 5B0?8 (482. B5:AB).

>;V@ @>7G8=C 20@VNT 2V4 A2VB;>-6>2B>3> 4> 1C@HB8=>2>3> 70;56=> 2V4 :=F5=B@0FVW,
@>7G8==8:0 B0 C<>2 715@V30==O. @8 4>B@8<0==V @5:><5=40FV9 4VO ?@5?0@0BC =5 70;568BL
2V4 20@V0FV9 9>3> 7010@2;5==O.

&5DB07848< C :=F5=B@0FVOE 2V4 1 <3/<; 4> 40 <3/<; AC

0,9 % @>7G8= =0B@VN E;>@84C; /6 @>7G8= =0B@VN ;0:B0BC; @>7G8= %0@B<0=0; 5 % @>7G8=
3;N:>78; 0,225 % @>7G8= =0B@VN E;>@84C B0 5 % @>7G8= 3;N:>78; 0,45 % @>7G8= =0B@VN
E;>@84C B0 5 % @>7G8= 3;N:>78; 0,9 % @>7G8= =0B@VN E;>@84C B0 5 % @>7G8= 3;N:>78;

0,18 % @>7G8= =0B@VN E;>@84C B0 4 % @>7G8= 3;N:>78; 10 % @>7G8= 3;N:>78; 10 % @>7G8=
3;N:>78 40 B0 0,9 % @>7G8= =0B@VN E;>@84C; 10 % @>7G8= 3;N:>78 40 B0 5 % @>7G8= 3;N:>78; 6
% @>7G8= 45:AB@0=C 70 B0 0,9 % @>7G8= =0B@VN E;>@84C; 6 % @>7G8= 45:AB@0=C 70 B0 5 %
@>7G8= 3;N:>78.

&5DB07848< C :=F5=B@0FVOE 2V4 0,05 <3/<; 4> 0,25 <3/<; ACN 4;O V=B@0?5@8B>=50;L=>3>
4V0;V7C (;0:B0B><).

&5DB07848< 4;O 2=CB@VH=L>< O7>2>3> 22545==O <>6=0 @>7G8=OB8 C 0,5 % 01> 1 % @>7G8=V
;V4>:0W=C 3V4@>E;>@84C.

D5:B82=VABL >1>E ?@5?0@0BV2 715@V30TBLO ?@8 7V 4 <3/<; 7 B0:8<8 @5G>28=0<8:
3V4@>:>@B87>= (3V4@>:>@B87>=C =0B@VN D>AD0B) 1 <3/<; C 0,9 % @>7G8=V =0B@VN
E;>@84C 4;O V=T:FV9 01> 0,5 % @>7G8=V 3;N:>78; F5DC@>:A8< (F5DC@>:A8< =0B@VN) 3 <3/<; C
0,9 % @>7G8=V =0B@VN E;>@84C 4;O V=T:FV9; ;>:A0F8;V= (:>:A0F8;V= =0B@VN) 4 <3/<; C 0,9 %
@>7G8=V =0B@VN E;>@84C 4;O V=T:FV9; 35?0@8= 10 /<; 01> 50 /<; C 0,9 % @>7G8=V =0B@VN
E;>@84C 4;O V=T:FV9; :0;VN E;>@84 10 <5:2/; 01> 40 <5:2/; C 0,9 % @>7G8=V =0B@VN E;>@84C 4;O
V=T:FV9.

=0 >@07848 T:FV9, <>6=0 4>40B8 4> @>7G8=C <5B@>=V407>;C (500 <3 C 100 <); ?@8 FL>18420
?@5?0@0B8 715@V30NBL A2>N 0:B82=VABL.

@83>BC20==O @>7G8=V2 4;O 2=CB@VH=L><O7>2>W 01> 2=CB@VH=L>25==>W 1>;NA=>W
V=□T:FVW:

1. :=>;B8 3>;:C H?@8F0 G5@57 :@8H:C D;0:=0 V 225AB8 @5:><5=4>20=89 >1 T< @>7G8==8:0.

2. 89=OB8 3>;:C H?@8F0 B0 AB@CA8B8 D;0:>= 4> >B@8<0==O ?@>7>@>3> @>7G8=C.
3. 5@525@=CB8 D;0:>=. @8 ?>2=VABN 22545=>@H=V H?@8F0 2AB028B8 3>;:C C D;0:>=. 01@0B8 25AL @>7G8= C H?@8F, ?@8 FL>;:0 25AL G0A ?>28==0 1CB8 C @>7G8=V.

@83>BC20==O @>7G8=V2 4;O 2=CB@VH=L>25==>W V=DC7VW (D;0:>= 1 3)

1. :>;>B8 3>;:C H?@8F0 G5@57 :@8H:C C D;0:>=0 V 225AB8 10 <; @>7G8==8:0.
2. 89=OB8 3>;:C H?@8F0 B0 AB@CA8B8 D;0:>= 4> >B@8<0==O ?@>7>@>3> @>7G8=C.
3. 5 2AB02;OB8 3>;:C 4;O ?>2VB@O 4> ?>2=>3> @>7G8=5==O ?@5?0@0BC. AB028B8 3>;:C 4;O ?>2VB@O G5@57 :@8H:C C D;0:>= 4;O ?>A;01;5==O 2=CB@VH=L>3> B8A:C C D;0:>=V.
4. 5 289<0NG8 3>;:C 4;O ?>2VB@O, 4>25AB8 7030;L=89 >1 T< 4> 50 <;. 89=OB8 3>;:C 4;O ?>2VB@O, AB@CA8B8 D;0:>= V =0;03>48B8 A8AB5

@8)>1 70157?5G8B8 AB5@8;L=VABL ?@5?0@0BC, 4C65 206;82> =5 2AB02;OB8 3>;:C 4;O ?>2VB@O G5@57 :@8H:C 4> @>7G8=5==O ?@5?0@0BC.

>B>289 @>7G8= <>6=0 715@V30B8 ?@>BO3<< 24 3>48= ?@8 B5 ?@>BO3<< 7 4=V2 ?@8 B5 4 °!.

VB8. 0AB>A>2C20B8 4VBO< 7 ?5@H8E 4=V2 68BBO.

5@54>7C20==O. 5@54>7C20==O <>65 ?@8725AB8 4> =52@>;>3VG=8E CA;:04=5=L, B0:8E O: 5=F5D0;>?0BVO, AC4<8 V :<0. !8<8 ?5@54>7C20==O <>6CBL 28=8:=CB8 C ?0FVT=BV2 V7 =8@:>2>N =54>AB0B=VABN, O:I> =5 7<5=H8B8 C =8E 2V4?>2V4=> 4>7C (482 @>74V;8 «!>AVI 70AB>AC20==O B0 4>78» B0 «A>1;82>ABV 70AB>AC20==O»). >=F5=B@0FVN F5DB0784820BFV :@>2V <>6=0 7<5=H8B8 H;OE>< 35<>4V0;V7C 01> ?5@8B>=50;L=>3> 4V0;V7C.

>1VG=V @50:FVW.

=D5:FVW B0 V=207VW

0=484>7 (2;:NG0NG8 203V=VB V 0DB>7=89 AB<0B8B).

@>2>=>A=0 B0 ;V

>78=>DV;VO, B@<1>F8B>7, ;59:>?5=VO, =59B@>?5=VO V B@<1>F8B>?5=VO, ;VF8B>7, 35 <>;VB8G=0 0=5F8B>7.

=0DV;0:AVO (2;:NG0NG8 1@>=E>A?07< B0/01> 0@B5@V0;L=C 3V?>B5=7VN).

5@2>20 A8AB5<0

0?0<>@>G5==O, 3>;>2=89 1V;L, ?0@5AB57VW.

>2V4><;O;>AO ?@> 28?04:8 =52@>;>3VG=8E CA;:04=5=L, B0:8E O: B@5<>@, ;;>=VO, AC4<8, 5=F5D0;>?0BVO B0 :><0 C E2>@8E V7 =8@:>2>N =54>AB0B=VABN, 4;O O:8E 4>70 F5DB078482V4=> 7 <5=H5=0.

!C48==V

?>@CH5==O

\$.51VB 01> B@><1>D;51VB C

(;C=:>2>-:8H:>2V ?>@CH5==O

V0@5O, =C4>B0, 1;N20==O, 1V;L C 682>BV B0 :>;VB.

/: V ?@8 70AB>AC20==V V=H8E F5D0;>A?>@8=V2, :>;VB <>65 1CB8 ?>2O70=89 7 *Clostridium difficile* V
<>65 ?@>O2;OB8AL C 283;O4V ?A524<5<1@0=>7=>3> :>;VBC (482. @>74V; «A>1;82>ABV
70AB>AC20==O»).

>@CH5==O A<0:C.

!5G>284V;L=0 A8AB5<0

=B5@AB8FV0;L=89 =5D@8B, 3>AB@0 =8@:>20 =54>AB0B=VABL.

5?0B>1V;V0@=V @50:FVW

"@0=78B>@=5 ?V428I5==O @V2=O >4=>3> 01> :V;L:>E ?5GV=:>28E D5@<5=BV2 (" , !", , , " , ;C6=0
D>AD0B070). □>2BO=8FO.

(:V@0 B0 ?V4H:V@=V B:0=8=8

0:C;>?0?C;L>7=89 28A8? 01> :@>?82O=:0, A25@1V6, 0=3V>=52@>B8G=89 =01@O:, ?>;V<>@D=0
5@8B5<0, A8=4@< !BV25=A0-6>=A>=0 B0 B>:A8G=89 5?V45@<0;L=89 =5:@>;V7.

030;L=V B0 @>7;048 C

V;L B0/01> 70?0;5==O C <O7>2>W V=T:FVW, 30@OG:0.

01>@0B>@=V ?>:07=8:8

>78B82=89 B5AB C<1A0, O: V ?@8 70AB>AC20==V 45O:8E V=H8E F5D0;>A?>@8=V2, V=:>;8
A?>AB5@V30;>AO B@0=78B>@=5 ?V428I5==O @V2=O A5G>28=8 :@>2V, 07>BC A5G>28=8 :@>2V
B0/01> :@50B8=V=C C A8@>20BFV :@>2V.

>78B82=0 @50:FVO C<1A0 A?>AB5@V30TBLAO ?@81;87=> C 5 % ?0FVT=BV2, I> <>65 2?;820B8 =0
287=0G5==O 3@C?8 :@>2V.

"5@ABV.3 @>:8.

#<>28 715@V30==O.

15@V30B8 ?@8 B5°! C 70E8I5=>

15@V30B8 C =54>ABC?=>

5AC □>@07848< <5=H AB01V;L=89 C @>7G8=V =0B@VN 1V:0@1>=0BC 4;O V=T:FV9, =V6 2 V=H8E
@>7G8=0E 4;O 2=CB@VH=L>25==>3> 22545==O, B><5=4CTBLAO O: @>7G8==8:.

&5DB07848< B0 03;V:>7848 =5 A;V4 74=V9 V=DC7V9=V9 A8AB5 H?@8FV.

!>AB5@V30;8AO 28?04:8 CB2>@5==O >A04C, :>;8 4> @>7G8=C F5DB078484020;8 20=!:<5=4CTBLAO
?@><820B8 V=DC7V9=V A8AB5<8 B0 2=CB@VH=L>25==V :0B5B5@8 @8AB0==O< F8E 42>E
?@5?0@0BV2.

#?0:>2:0.

> 1 D;0:>=C C :0@B>==V9 :>@>1FV.

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

8@>1=8:

:AV@ \$0@<0ALNB8:0; >

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VAF57=0E>465==O .

2-89 :< V=3 >C4, >@C465@4 69189, @0=,

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