

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

"-&/
(METOCLOPRAMIDE-DARNITSA)

!,:04:
4VNG0 @5G>28=0: metoclopramide;
1 <; @>7G8=C E;>@84C 5 <3;
4>?>28=8: =0B@VN E;>@84, 48=0B@VN 545B0B, =0B@VN AC;LDVB 1572>4=89 (221),
?@>?V;5=3;V:>;L, :8A;>B0 E;>@8AB>2>4=520 @>72545=0, 2>40 4;O V=T: FV9.

V:0@AL:0 D>@<0. >7G8= 4;O V='T: FV9.

\$0@<0:>B5@0?52B8G=0 3@C?0. !B8@8 ?5@8AB0;LB8:8 (?@>?C;LA0=B8).
>4 " ! 03F 01.

;V=VG=V E0@0:B5@8AB8:8.
>:070==O.

4>@>A;8E □ 4;O 70?>1V30==O ?VA;O>?5@0FV9=>W =C4>B8 V 1;N20==O; =C4>B8 V 1;N20==O,
28::8:0=8E @04V>B5@0?VTN; 2V4AB@>G5=>W (=5 3>AB@>W) =C4>B8 V 1;N20==O, 28::8:0=8E EV
B5@0?VTN; 0 B0:>6 4;O A8<0B8G=>3> ;V:C20==O =C4>B8 V 1;N20==O, 2::;NG0NG8 BV, I> ?>2'O70=V 7
3>AB@>N
4VB59 □ O: ?@5?0@0B 4@C3>W ;V=VW 4;O ?@>DV;0:B8:8 2V4AB@>G5=8E =C4>B8 V 1;N20==O,
28::8:0=8E EVB5@0?VTN, B0 4;O ;V:C20==O =0O2=>W ?VA;O>?5@0FV9=>W =C4>B8 V 1;N20==O.
@5?0@0B 701>@>=5=> 70AB>A>2C20B8 C 4VB59 <>;>4H8E 1 @>:C.

@>B8?>:070==O.
i428I5=0 GCB;82VABL4> <5B>;;>?@0 4> 1C4L-O:>W V=H>W A;;04>2>W ?@5?0@0BC;
H;C=>2>:-8H:>20 :@>2>B5G0;
<5E0=iG=0 :8H:>20 =5?@>EV4=VABL;
H;C=>2>:-8H:>20 ?5@D>@0FiO;
?V4B25@465=0 01> 70?V4>7@5=0 D5>E@><>F8B><0 (G5@57 @878: BO6:8E =0?04V2
0@B5@V0;L=>W 3V?5@B5=7VW);
?V7=O 48A:V=57VO, 7C<>2;5=0 =59@>;5?B8:0<8 01> <5B>;;>?@0<, 2 0=0<=57V;
5?V;5?AVO(?V428I5==O G0AB>B8 B0 V=B5=A82=>ABV ?@8ABC?V2);
E2>@>10 0@:V=A>=0;
AC?CB=T 70AB>AC20==O 7 ;52>4>?>N G8 4>?0
2AB0=>2;5=0 <5B35<>3>;1V=5AC20==V <5B>;;>?@0 45DVF8BV -F8B>E@>;
?@>;0:B8=70;56=V ?CE;8=8;
?i428I5=0 AC4><=0 3>B>2=iABL (5:AB@0?i@0<i4=i @CE>2i @>7;048);
4VB8 2V:< 4> 1 @>:C G5@57 @878: @>728B:C 5:AB@0?V@0@CH5=L.
72O7:C 7 2< AC;LDVBC =0B@VN ?@5?0@0B =5 <>6=0 ?@87=0G0B8 E2>@8< =0 1@>=EV0;L=C 0AB
N GCB;82VABN 4> AC;LDVBC.

!?!>AVI 70AB>AC20==O B0 4>78.
>7G8= 4;O V=T: FV9 70AB>A>2C20B8 2=CB@VH=L<O7> 01> 2=CB@VH=L>25==> C 283;O4V
?>2V;L=>W 1>;NA=>W V=T: FVW ?@>BO3< I>=09<5=H5 3-E E28;8=.
O:>ABV @>7G8==8:0 70AB>A>2C20B8 0,9 % @>7G8= =0B@VN E;>@84C, 5 % @>7G8= 3;N:>78.
>@>A,8
@5?0@0B ?@87=0G0B8 C 4>7V 10 <3 4> 3-E @07V2 =0 4>1C. 0:A8<0;L=0 4>1>20 4>70 AB0=>28BL 30
<3 01> 0,5 <3/:3 <0A8 BV;0.
0AB>AC20==O V=T: FV9=8E D>@< <0T 2V41C20B8AO ?@>BO3< O:><>30 :>@>BH>3> ?@><>30 H284
H8< ?5@5E>4>< =0 70AB>AC20==O ?5@>@0;L=8E 01> @5:B0;L=8E D>@< <5B>;;>?@0
VBO

@8 70AB>AC20==V 4;O 70?>1V30==O ?VA;O>?5@0FV9=>W =C4>B8 V 1;N20==O<5B>;>?@0
A>2C20B8 ?VA;O 70:V=G5==O >?5@0FVW.
5:<5=4>20=0 4>70 <5B>;>?@028BL 0,1-0,15 <3/:3 <0A8 BV;0 4> 3 @07V2 =0 4>1C. 0:A8<0;L=0 4>1>20
4>70 AB0=>28BL 0,5 <3/:3 <0A8 BV;0. /:I> =5>1EV4=> ?@>4>268B8 70AB>AC20==O ?@5?0@0BC, A;V4
4>B@8
!E5<0 4>7C20==O

V:, @>:8	0A0 BV;0, :3	4=>@07>20 4>70, <3	'0AB>B0
1-3	10-14	1	> 3 @07V2 =0 4>1C
3-5	15-19	2	> 3 @07V2 =0 4>1C
5-9	20-29	2,5	> 3 @07V2 =0 4>1C
9-18	30-60	5	> 3 @07V2 =0 4>1C
15-18	>60	10	> 3 @07V2 =0 4>1C

0:A8<0;L=0 B@820;VABL 70AB>AC20==O<5B>;>?@02AB0=>2;5=>W ?VA;O>?5@0FV9=>W =C4>B8 V
1;N20==O AB0=>28BL 48 3>48=
0:A8<0;L=0 B@820;VABL 70AB>AC20==O<5B>;>?@04;O 70?>1V30==O 2V4AB@>G5=>W =C4>B8 V
1;N20==O, A?@8G8=5=8E EVB5@0?VTN, AB0=>28BL 5 4V1.
0FVT=B0< 7 ?>@CH5==O< DC=:FVW =8@>:
E2>@8E 7 B5@N AB04VTN ?>@CH5==O DC=:FVW =8@>: (:;V@5=A :@50B8=V=C ≤15 <;/E2) 4>7C
<5B>;>?@01EV4=> 7<5=H8B8 =0 75 %.
E2>@8E 7 ?>1EV4=> 7<5=H8B8 =0 50 %.
0FVT=B0< 7 ?5GV=:>2>N =54>AB0B=VABNC=0A;V4>: 71V;LH5==O ?5@V>4C =0?V2282545==O
70AB>A>2C20B8 ?>;>28==C 4>7C.
0FVT=B8 ;VB=L>3> 2V:C.
!;V4 @>73;O=CB8 <>6;82VABL 7<5=H5==O 4>78 C E2>@8E ;VB=L>3> 2V:C 2=0A;V4>: 7=865==O
DC=:FVW =8@>: B0 ?5GV=:8, 7C<>2;5=8E 2V:>
"@820;VABL ;V:C20==O.
<5B>N 72545==O 4> 1VG=8E @50:FV9 7 1>:C =5@2>2>W A8AB5<8 B0 V=H8E ?>1VG=8E @50:FV9
?@5?0@0B A;V4 70AB>A>2C20B8 BV;L:8 4;O :>@>B>B@820;>3> ;V:C20==O (4> 5 4V1).

>1VG=V @50:FVW.
I>:C A8AB5<8 :@>2V B0 ;VW A8AB5<8: <5B35<>3>;>1V=5b5-@54C:B078, >A>1;82> C =5<>2;OB,
AC;LD35<>3>;>1V=52'O70=0, 3>;>2=8< G8=><, V7 AC?CB=V< 70AB>AC20==O< 28A>:8E 4>7
?@5?0@0BV2, I> 282V;L=ONBL AV@:C.
I>:C A5@F52>-AC48==>W A8AB5<8: 1@048:0@4VO, >A>1;82> ?@8 2=CB@VH=L>25==>AC20==V,
7C?8=:0 A5@FO ?@>BO3< :>@>B>:3> G0AC ?VA;O V='T:FVW, O:0<>65 1CB8 =0A;V4:<<
1@048:0@4VW, 0B@V>25=B@8:C;O@=0 1;>:040, 1;>:040 A8=CA>2>3> 2C?0, >A>1;82> ?@8
2=CB@VH=L>25==>AC20==V, ?@>;>=30FVO V=B5@20;CQT, H;C=>G>20 B0EV:0@4VO B8?C
«?V@C5B», 0@B5@V0;L=0 3V?>B5=7VO, H>;, A8=:>?5 ?@8 2=CB@VH=L>25==>AB@0 0@B5@V0;L=0
3V?5@B5=7VO C ?0FVT=BV2 7 D5>E@><>F8B><N.
0@5TAB@>20=> >:@52V4><;5==O I>4> <>6;82>ABV @>728B:C BO6:8E A5@F52>-AC48==8E @50:FV9,
>1C<>2;5=8E 70AB>AC20==O< <5B>;>?@0A>1;82> ?@8 2=CB@VH=L>25==>
I>:C =5@2>2>W A8AB5<8:
5:AB@0?V@0, 48AB>=VW (C B> 28?04:8 48A:i=5B8G=>3> A8=4@>A>1;82> C 4VB59 B0
?0FVT=BV2 2V:< 4> 30 @>:V2, @878: O:8E 71V;LHCNBLAO ?@8 ?5@528I5==V 4>1>2>W 4>78
0,5 <3/:3 <0A8 BV;0: A?07< 1;8GGO, B@87<, @8BB@C7VO O78:0, 1C;L10@=89 B8? <>2;5==O,
A?07< 5:AB@0>:C;O@=8E <07V2, 2;;NG0NG8 >:C;>3V@=V :@878, =5?@8@>4=V ?>;>65==O
3>;>28 B0 ?;5G59, >?VAB>B>=CA, <07>289 3V?5@B>=CA;
?0@:i=A>=i7< (B@5<>@, ?>A<8:C20==O <07i2, 1@048:V=57VO, @83V4=VABL<07V2,
<0A>:>?4V1=5 >1;8GGO) ?iA;O B@820;>3> ;i:C20==O <5B>;>?@0< C 45O:8E ?0FVT=BV2
;VB=L>3> 2i:C, 0 B0>6 ?@8 =8@>:2V9 =54>AB0B=>ABV;
?V7=O 48A:V=57VO, I> <>65 1CB8 =572>@>B>=N, <>65 28=8:0B8 ?@8 B@820;V9 B5@0?VW
<5B>;>?@0<, 2 >A>=>2=>3> 2V:C (>A>1;82> 6V=>:), C ?0FVT=BV2 7 FC:@>28< 4V015B< V
70728G09 @>72820TBLAO ?VA;O 2V4O2;OTBLAO <8<>2V;L=8<8 @CE0<8 O78:0, >1;8GGO,
@>B0, I5;5?8, V=>4V <8<>2V;L=8<8 @CE0<8 BC;C10 V/01> :V=V2>;;

=59@>;5?B8G=89 7;>O:VA=89 A8=4@<×, I> 2::NG0T 3V?5@?V@5:AVN, 72> @>7?>G0B8
;V:C20==O (40=B@>;5=, 1@><@:8?B8=);
3>;>2=89 1V;L; 70?0<>@>G5==O; A>;82VABL; ?>GCBBO 2B<×8; 2V4GCBBO AB@0EC;
@>73C1;5=VABL; HC< C 2CE0E.
"0:>6 VA=CT @878: 3>AB@8E (:>@>B:>G0A=8E) =52@>;>3VG=8E @>7;04V2, I> 28I89 C 4VB59.
A8EVG=V @>7;048: 45?@5AVO, 30;NF8=0FVW, A?;CB0=VABL A2V4×>ABV, B@82>6=VABL,
=5A?>:V9.
I>:C B@02=>3> B@0:BC: =C4>B0, 48A?5?AVO, ACEVABL C @>BV, 70?>@. @8 70AB>AC20==i
<5B>;;>?@070E, 28I8E 70 4>1>2C C E2>@8E <>65 28=8:0B8 4V0@50.
I>:C VW A8AB5<8, H:V@8 B0 ?V4H:V@=>W .;VB:>28=8: @50:FVW 3V?5@GCB;82>ABV, 7>:@5<0:
H:V@=V 28A8?0==O, 3V?5@5?82O=:0, =01@O: 2V=:5, 0=0DV;0:B8G=V @50:FVW, 2::NG0NG8
0=0DV;0:B8G=89 H>:. '5@57 2@B8, 1;N20==O, A28ABOG>3> 48E0==O, 3>AB@>3> =0?04C 0AB<8,
?>@CH5==O A2i4<>ABi a l o H>:C. &i @50:FiW <>6CBL <0B8 i=482i4C0;L=89 ?5@51V3.
I>:C @5?@>4C:B82=>W A8AB5<8 B0 <>;>G=8E 70;>7: ?iA;O 1i;LH B@820;>W B5@0?VW
?@5?0@0B<×, C 72?07:C 7i AB8<0ABiO, 30;0:B>@50 01> ?>@CH5==O <5=AB@C0;L=>3> F8;;C, 0
<5=>@50; ?@8 @>728B:C F8E O28I 70AB>AC20==O <5B>;;>?@0
01>@0B>@=V 4>A;V465==O: ?V428I5==O @V2=O 5=78
030;L=V @>7;048: 0AB5=VO, ?V428I5=0 2B<×;N20=VABL.
?i4;iB:i2 i E2>@8E V7 BO6:8<8 ?>@CH5==O<8 DC=:FiW =8@>: (=8@>:20 =54>AB0B=iABL),
2=0A;V4>: O:8E ?>A;01;NTBLAO 282545==O <5B>;;>?@0A>1;82> C206=> AB568B8 70 @>728B:<× ?>1i
G=8E O28I. # @07V WE 28=8:=5==O 70AB>AC20==O ?@5?0@0BC >4@07C 6 ?@8?8=8B8.
878: @>728B:C ?>1VG=8E @50:FV9 7 1>:C =5@2>2>W A8AB5<8 7@>AB0T ?@8 70AB>AC20==V
?@5?0@0BC C 28A>:8E 4>70E B0 ?@8 B@820;>AC20==V.

5@54>7C20==O.

!8<8: A>;82VABL, 7=865==O @V2=O A2V4<×>ABV, A?;CB0=VABL A2V4×>ABV, 4@0BV2;82VABL,
=5A?>:V9 B0 9>3> ?>A8;5==O, AC4<×8, 5:AB@0?V@0-<>B>@=V @>7;048, ?>@CH5==O DC=:FVW
A5@F52>-AC48==>W A8AB5<8 7 1@048:0@4VTN V ?V428I5==O< G8 7=865==O< 0@B5@V0;L=>3>
B8A:C, 30;NF8=0FVW, 7C?8=:0 48E0==O V A5@F52>W 4VO;L=>ABV, 48AB>=VG=V @50:FVW>2V4>
<×;O>;AO ?@> ?>>48=>:V 28?04:8 <5B35<>3>;>1V=5
V:C20==O: 5:AB@0?V@07;048 CAC20NBL ?>2V;L=8< 2=CB@VH=L>25==8< 22545==O< 0=B84>BC
1V?5@845=C. # 28?04:C 70AB>AC20==O 25;8:8E 4>7 <5B>;;>?@03> =5>1EV4=> 2840;8B8 7V H;C=:>2>-
:8H:>2>3> B@0:BC H;OE<× ?@><820==O H;C=:0 01> ?@89=OB8 0:B82>20=5 2C3V;;O B0 AC;LD0B
=0B@VN. 0 68BBT2> 206;828<8 DC=:FVO<8 >@30=V7AB5@V30B8 4> ?>2=>3> 7=8:=5==O A8
B@CT==O.

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

03VB=VABL.

5;8:0 :V;L:VABL 40=8E, >B@8<0=8E 7 CG0ABN 203VB=8E 6V=>: (?>=04 1000 @57C;LB0BV2 V7
70AB>AC20==O< ?@5?0@0BC), 2:07CT =0 2V4ACB=VABL 6>4=>W B>:A8G=>ABV, I> ?@872>48BL 4>
<0;LD>@<0FV9 01> D5B>B>:A8G=>ABV. 5B>;;>?@0ABV =5 <>6=0 28;;NG0B8 ?>O2C 5:AB@0?V@03>
A8=4@>2>=0@>465=>3>. 5>1EV4=> C=8:0B8 70AB>AC20==O <5B>;;>?@0ABV. @8 70AB>AC20==V
<5B>;;>?@0B@V1=> A?>AB5@V30B8 70 =>2>=0@>465=8
>4C20==O 3@C44N.

5B>;;>?@0ABV ?@>=8:0T C 3@C4=5 <>;>: . "×5=4CTBLAO 70AB>A>2C20B8 <5B>;;>?@04C20==O
3@C44N. 5>1EV4=> @>73;O=CB8 <>6;82VABL ?@8?8=5==O 70AB>AC20==O<5B>;;>?@0C 6V=>:, O:V
3>4CNBL 3@C44N.

VB8.

5B>;;>?@0B8?>:070=89 4VBO< 2V:<× 4> 1 @>:C.

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

52@>;>3VG=V?>@CH5==O.

>6CBL A?>AB5@V30B8AO 5:AB@0?V@0@CH5==O, >A>1;82> C 4VB59, V/01> ?@8 70AB>AC20==V
28A>:8E 4>7. &V @50:FVW 70728G09 A?>AB5@V30NBLAO =0 ?>G0B:C ;V:C20==O B0<>6CBL
28=8:0B8 ?VA;O >4=>@07>2>3> 70AB>AC20==O. # 28?04:C @>728B:C 5:AB@0?V@0B@V1=> =5309=>
2V4< FV 5D5:B8 ?VA;O ?@8?8=5==O ;V:C20==O ?>2=VABN 7=8:0NBL, 0;5<>6CBL 28<030B8 A8
<0B8G=>3> ;V:C20==O (15=7>4V075?V=8 C 4VB59 V/01> 0=B8E>;V=5@3VG=V
?@>B8?0@:V=A>=VG=V ;V:0@AL:V 70A>18 C 4>@>A;8E).
V6 :>6=8< 22545==O< <5B>;;>?@0@3=5==O 4>78, I>1 C=8:=CB8 ?5@54>7C20==O, =5>1EV4=> 4>B@8
I>=09<5=H5 6-3>48==>3> V=B5@20;C.
"@820;5 ;V:C20==O <5B>;;>?@0< <>65 ?@872>48B8 4> ?V7=L>W 48A:V=57VW, I> ?>B5=5V9=> T
=572>@>B=>N, >A>1;82> 2>AV1 ;VB=L>3> 2V:C. V:C20==O =5<0T B@820B8 1V;LH5 3 2 G5@57 @878:
@>728B:C ?V7=L>W 48A:V=57VW. V:C20==O =5>1EV4=> ?@8?8=8B8, O:I> 7O2;ONBLAO ;;V=VG=V
>7=0:8 ?V7=L>W 48A:V=57VW.
@8 70AB>AC20==V <5B>;;>?@02 :<<1V=0FVW 7 =59@>;5?B8:0<8, 0 B0:>6 ?@8 <>=>B5@0?VW
<5B>;;>?@0< ?>2V4<;<;O;>AO ?@> @>728B>: 7;>O:VA=>3> =59@>;5?B8G=>3> A8=4@>. # 28?04:C
28=8:=5==O A8O:VA=>3> =59@>;5?B8G=>3> A8=4@>AC20==O <5B>;;>?@01EV4=> =5309=>
?@8?8=8B8 B0 ?>G0B8 2V4?>2V4=5 ;V:C20==O.
?0FVT=5V2 V7 AC?CB=V<8 =52@>;>3VG=8<8 70E2>@N20==O<8 B0 C ?0FVT=5V2, O:V >B@8
1EV4=> 1CB8 >A>1;82> >15@56=8<8.
@8 70AB>AC20==V <5B>;;>?@0

5B35<>3;>1V=5

>2V4><;O;>AO ?@> 28?04:8 <5B35<>3;>1V=5 >AB0B>G=> ?@8?8=8B8 ?@89>< <5B>;;>?@02V4=V
70E>48 (=0?@8::04, ?@89>< <5B8;5=>2>3> A8=L>3>).
!5@F52V @>7;048.
>2V4><;O;>AO ?@> B06:V ?>1VG=V @50:FVW 7 1>:C A5@F52>-AC48==>W A8AB5<8, 2;;NG0NG8
28?04:8 3>AB@>W AC48==>W =54>AB0B=>ABV, B06:>W 1@048:0@4VW, 7C?8=:8 A5@FO B0
?>4>265==O V=B5@20;C QT, O:V A?>AB5@V30;8AO ?VA;O ?@89>@=CB@VH=L>25==> ?@5?0@0B
A;V4 22>48B8 H;OE>< ?>2V;L=>W 1>;NA=>W V=T:FVW (
>@CH5==O DC=:FVW =8@>: B0 ?5GV=:8.
0FVT=B0< V7 ?>@CH5==O< DC=:FVW =8@>: 01> B06:8< ?>@CH5==O< DC=:FVW ?5GV=:8 @5:>
<5=4CTBLAO 7<5=H5==O 4>78.
!;V4 7>A>1;82>N >15@56=VABN 70AB>A>2C20B8 ?@5?0@0B C ?0FVT=5V2 3@C? @878:C, 0 A0<5 C
?0FVT=5V2 ;VB=L>3> 2V:C, V7 @>7;040<8 A5@F52>W ?@>2V4=>ABV, 7 =5A:>@83>20=8<
48A10;0=A>< 5;5:B@>;VBV2 01> 1@048:0@4VTN, B0 ?0FVT=5V2, O:V ?@89<0NBL V=HV
?@5?0@0B8, I> ?>4>26CNBL V=B5@20; QT. @5?0@0B =5 A;V4 70AB>A>2C20B8 4;O ;V:C20==O
E@>=VG=8E 70E2>@N20=L, B0:8E O: 30AB@>?0@57, 48A?5?AVO V 30AB@>57>D0350;L=0
@5D;N:A=0 E2>@>10, G8 O: 4>40B:>289 70AV1 ?@8 ?@>2545==V EV@C@3VG=8E 01>
@04V>;>3VG=8E ?@>F54C@.

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.

@8 70AB>AC20==V ?@5?0@0BC A;V4 CB@8<0B8AL 2V4 ?>B5=5V9=> =5157?5G=8E 284V2
4VO;L=>ABV, I> 28<030NBL ?V428I5=>W C2038 (:5@C20==O 02B>B@0=A?>@B>, @>1>B0 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.

@>B8?>:070=V :<<1V=0FVW.

52>4>?0 01> 4>?0=VAB8 B0<5B>;;>?@0

<<1V=0FVW, O:8E A;V4 C=8:0B8.

;;>3>;L ?>A8;NT A540B82=C 4VN <5B>;;>?@0

<<1V=0FVW, =0 O:V A;V4 725@=CB8 C203C.

@8 >4=>G0A=>AC20==V 7 ?5@>@0;L=8<8 ;V:0@AL:8<8 70A>10<8, =0?@8::04 ?0@0F5B0<>;<, <5B>;;>?@0

=B8E>;V=5@3VG=V 70A>18 B0 ?>EV4=V<>@DV=C: 0=B8E>;V=5@3VG=V 70A>18 B0 ?>EV4=V
<>@DV=C E0@0:B5@87CNBLAO 270T<=8< 0=B03>=V7<> V7 <5B>;>?@0< AB>A>2=> 2?;82C =0
<>B>@=C 0:B82=VABL B@02=>3> B@0:BC.
=3V1VB>@8 F5=B@0;L=>W =5@2>2>W A8AB5<8 (?>EV4=V<>@DV=C, =59@>;5?B8:8, A540B82=V
0=B83VAB0:0B>@8 @5F5?B>@V2 H₁, A540B82=V 0=B845?@5A0=B8, 10@1VBC@0B8, ;>=V48= B0
A?>@V4=5=V ?@5?0@0B8): ?>B5=FVNNBL 4VN<5B>;>?@0
59@>;5?B8:8: C @07V 70AB>AC20==O <5B>;>?@0<1V=0FVW 7 V=H8<8 =59@>;5?B8:0<8 <>65
28=8:0B8 :CO20 5:AB@0?V@07;04V2.
!5@>B>=V=5@3VG=V ?@5?0@0B8: 28:>@8AB0==O <5B>;>?@0<1V=0FVW V7
A5@>B>=V=5@3VG=8<8 ?@5?0@0B0<8, =0?@8:;04, A5;5:B82=8<8 V=3V1VB>@0<8 72>@>B=>3>
70E>;5==O A5@>B>=V=C (!) <>65 ?V428I8B8 @878: @>728B:C A5@>B>=V=>2>3> A8=4@>
83>:A8=: <5B>;>?@02V.
?>A?>@8=: <5B>;>?@04>ABC?=VABL F8:;>A?>@8=C (C_{max}=0 46 % B0 2?;82 =0 22 %). 5>1EV4=>
?@>2>48B8 @5B5;L=89 <=>VB>@8=3 :>=F5=B@0FVW F8:;>A?>@8=C 2 ?;072V. ;V=VG=V =0A;V4:8
FL>3> O28I0 >AB0B>G=> =5 287=0G5=V.
V20:C@V9 B0 AC:A0<5B>=V9: V='T:FVO<5B>;>?@0
>BC6=V V=3V1VB>@8 CYP2D6: @V2=V 5:A?>78FVW <5B>;>?@04=>G0A=>3> 70AB>AC20==V 7
A8;L=8<8 V=3V1VB>@0<8 CYP2D6, =0?@8:;04, D;C>:A5B8=>< V ?0@>:A5B8=>G0 ;V=VG=0
7=0GCIVABL FL>3> B>G=> =52V4<0, 70 ?0FVT=B0<8 =5>1EV4=> ?@>2>48B8 A?>AB5@565==O =0
?@54<5B ?>1VG=8E @50:FV9.
5B>;>?@0 <>65 ?>4>268B8 4VN AC:F8=V;E>;V=C.
72'O7:C 7 2< 2 i='T:Fi9=>7G8=i AC;LDiBC =0B@iN, Bi0I), ?@89=OB89 >4=>G0A=> 7 <5B>;>?@0<,
<>65 H284:> @>7I5?;N20B8AO 2 >@30=i7

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

\$0@<0:>48=0

5B>;>?@028< 0=B03>=VAB<, O:89 B0:>6 28O2;OT ?5@8D5@8G=C E>;V=5@3VG=C 0:B82=VABL.
V47=0G0NBL 420 >A=>2=8E 5D5:B8 ?@5?0@0BC: ?@>B81;N20;L=89 B0 5D5:B ?@8A:>@5==O
28?>@>6=5==O H;C=:0 B0 ?@>E>465==O :@V7L B>=:C :8H:C.
@>B81;N20;L=89 5D5:B 28;;8:0=89 4VTN =0 F5=B@0;L=C B>G:C AB>21C@>2>W G0AB8=8 <>7:C (E5
<>@5F5?B>@8 0:B82CNG0 7>=0 1;N20;L=>3> F5=B@C), V<>2V@=>, G5@57 30;L?0=V2.
>A8;5==O ?5@8AB0;LB8:8 B0:>6 G0AB:>2> :>=B@>;NTBLAO 28I8<8 F5=B@0<8, 0;5 B0:>6 G0AB:>2>
<>65 1CB8 704VO=89 <5E0=V7< ?5@8D5@8G=>W 4VW @07< 7 0:B820FVTN ?>AB30=3;V>=0@=8E
E>;V=5@3VG=8E @5F5?B>@V2 V, <>6;82>, ?@83=VG5==O< 4>?0@V2 H;C=:0 B0 B>=:>W :8H:8. '5@57
3V?>B0;0>@48=CT @CE>2C 0:B82=VABL 25@E=L>3> 2V44V;C H;C=:>2>:-8H:>2>3> B@0:BC:
?V428ICT B>=CA H;C=:0 V :8H5G=8:C, ?@8A:>@NT 28?>@>6=5==O H;C=:0, 7<5=HCT 30AB@>AB07,
?5@5H:>460T ?V;>@8G=>D0350;L=>@<0;V7CT 284V;5==O 6>2GV, 7<5=HCT A?07< ADV=:B5@0 44V,
=5 73> B>=CA, CAC20T 48A:V=57VN 6>2G=>3>
51060=V 5D5:B8 ?>H8@NNBLAO 3>;>2=8< G8=>< =0 5:AB@0?V@0@-1;>:CNG>W 4VW =0
F5=B@0;L=C =5@2>2C A8AB5

"@820;5 ;V:C20==O <5B>;>?@0< <>65 28;;8:0B8 7@>AB0==O :>=F5=B@0FVW ?@>;0:B8=C 2

A8@>20BFV :@>2V 2=0A;V4>: 2V4ACB=>ABV 4>?03> 30;L;0:B8=C. # 6V=>: >?8A0=V 28?04:8
30;0:B>@5W B0 ?>@CH5==O <5=AB@C0;L=>3> F8;;C, C G>;>2V:V2 3V=5:<0ABVO. 4=0: FV A8<8
7=8:0;8 ?VA;O ?@8?8=5==O ;V:C20==O.
\$0@<0:>: V=5B8:0.
>G0B>: 4VW =0 H;C=:>2>:-8H:>289 B@0:B 2V47=0G0TBLAO G5@57 1-3 E28;8=8 ?VA;O
2=CB@VH=L>25==>3> 22545==O V G5@57 10-15 E28;8= ?VA;O 2=CB@VH=L<'O7>2>3> 22545==O.
=B85<5B8G=0 4VO 715@V30TBLAO ?@>B03>< 12 3>48=. 1V;;0<8 ?;07<8 :@>2V 72O7CTBLAO 13-30 %
?@5?0@0BC. 1T< @>7?>4V;C 3,5 ;/:3. @>=8:0T :@V7L 35<0B>5=F5D0;VG=89 V ?;0F5=B0@=89
10@T@8, 284V;OTBLAO C 3@C4=5 <>;>: 5B01>;V7CTBLAO C ?5GV=FV. 5@V>4 =0?V2282545==O 4-
6 3>48=. '0AB8=0 4>78 (1;87L:> 20 %) 282>48BLAO C ?>G0B:>2V9 D>@ 80 %) ?VA;O<5B01>;VG=8E
?5@5B2>@5=L ?5GV=:>N 282>48BLAO =8@:0<8 C A?>;C:0E V7 3;N:C@>=>2>N 01> AV@G0=>N
:8A;>B>N.

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

A=>2=V DV78:>-EVABV: ?@>7>@0 15710@2=0 @V48=0.

5AC
='T:Fi9=89 @>7G8=<5B>;>?@0

"5@ABV.4 @>:8.

#<>28 715@V30==O.
15@V30B8 C =54>ABC?=>@83V=0;L=V9 C?0:>2FV ?@8 B5@>6C20B8.

#?0:>2:0.
> 2 <; 2 0 5 0=BC@=V9 G0@C=:>2V9 C?0:>2FV; ?> 1 01> ?> 2 :>=BC@=V G0@C=:>2V C?0:>2:8 C
?0GFV; ?> 10 0=BC@=V9 G0@C=:>2V9 C?0:>2FV; ?> 1 :>=BC@=V9 G0@C=:>2V9 C?0:>2FV C ?0GFV;
?> 10 0@>1FV.

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

8@>1=8:.
@" «\$0@<0F52B8G=0 DV@<0 «0@=8FO».

VAF57=0E>465==O.
#:@0W=0, 02093, <. 8W2, 2C;.>@8A?i;LAL:0, 13.

!" #&/
?> <548F8=A:>

"-&
(METOCLOPRAMIDE-DARNITSA)

!>AB02:
459AB2CNI55 25I5AB2>: metoclopramide;
1 <; @0AB2>@0 A>45@68B <5B>;>?@0<840 384@>E;>@840 5 <3;
2A?><>30B5;L=K5 25I5AB20: =0B@8O E;>@84, 48=0B@8O M45B0B, =0B@8O AC;LD8B 1572>4=K9
(221), ?@>?8;5=3;8>;L, :8A;>B0 E;>@8AB>2>4>@>4=0O @072545==0O, 2>40 4;O 8=J5:F89.

5:0@AB25==0O D>@<0. 0AB2>@ 4;O 8=J5:F89.

\$0@<0:>B5@0?52B8G5A:0O 3@C??0. !B8@K ?5@8AB0;LB8:8 (?@>?C;LA0=BK).
>4 " ! 03F 01.

;8=8G5A:85 E0@0:B5@8AB8:8.
>:070=8O.
27@>A;KE 4;O ?@54>B2@0I5=8O ?>A;5>?5@0F8>==>9 B>H=>BK 8 @2>BK, B>H=>BK 8 @2>BK,
2K720==KE @048>B5@0?859, >BA@>G5==>9 (=5 >AB@>9) B>H=>BK 8 @2>BK, 2K720==KE E8
<8>B5@0?859, 0 B0:65 4;O A8<0B8G5A:>3> ;5G5=8O B>H=>BK 8 @2>BK, 2;NG0O B5, GB> A2O70=K
A >AB@>9 <83@5=LN.

45B59 :0: ?@5?0@0B 2B>@>9 ;8=88 4;O ?@>D8;0:B8:8 >BA@>G5==KE B>H=>BK 8 @2>BK, 2K720==KE E8<8>B5@0?859, 8 4;O ;5G5=8O 8<5NI59AO ?>A;5>?5@0F8>==>9 B>H=>BK 8 @2>BK. @5?0@0B 70?@5I5=> ?@8<5=OBL C 45B59 <;04H5 1 3>40.

@>B82>?>:070=8O.

>2KH5==0O GC2AB28B5;L=>ABL :<5B>;;>?@0<84C 8;8 : ;N1>9 4@C3>9 A>AB02;ONI59 ?@5?0@0B0; 65;C4>G=>-:8H5G=>5 :@>2>B5G5=85; <5E0=8G5A:0O :8H5G=0O =5?@>E>48<>ABL; 65;C4>G=>-:8H5G=0O ?5@D>@0F88; ?>4B25@645==0O 8;8 70?>4>7@5==0O D5>E@><>F8B><0 (87-70 @8A:0 BO65;KE ?@8ABC?>2 0@B5@80;L=>9 38?5@B5=788); ?>74=OO 48A:8=578O, >1CA;>2;5=0 =59@>;5?B8:0<8 8;8 <5B>;;>?@0<84><, 2 0=0<=575; M?8;5?A8O (?>2KH5=85 G0AB>BK 8 8=B5=A82=>AB8 ?@8ABC?>2); 1>;57=L 0@:8=A>=0; >4=>2@5<5==>5 ?@8<5=5=85 A ;52>4>?>9 8;8 4>?0<8=5@38G5A:8<8 03>=8AB0<8; CAB0=>2;5==0O <5B35<>3;>18=5<8O ?@8 ?@8<5=5=88 <5B>;;>?@0<840 8;8 45D8F8B5 -F8B>E@> ?@>;0:B8=7028A8 >?CE>;8; ?>2KH5==0O AC4>@>6=0O 3>B>2=>ABL (M:AB@0?8@0<84=K5 42830B5;L=K5 @0AAB@>9AB20); 45B8 2 2>7@0AB5 4> 1 3>40 87-70 @8A:0 @0728B8O M:AB@0?8@0<84=KE =0@CH5=89. A2O78 A A>45@60=85< AC;LD8B0 =0B@8O ?@5?0@0B =5;L7O =07=0G0BL 1>;L=K< 1@>=E80;L=>9 0AB<>9 A ?>2KH5==>9 GC2AB28B5;L=>ABLN : AC;LD8BC.

!/?>A>1 ?@8<5=5=8O 8 4>7K.

0AB2>@ 4;O 8=J5:F89 22>48BL 2=CB@8 8;8 2=CB@825==> 2 2845 <54;5==>9 1>;NA=>9 8=J5:F88 =0 ?@>BO65=88 =5 <5=55 3-E <8=CB. :0G5AB25 @0AB2>@8B5;O 8A?>;L7>20BL 0,9 % @0AB2>@ =0B@8O E;>@840, 5 % @0AB2>@ 3;N:>7K. 7@>A;K @5?0@0B =07=0G0BL 2 4>75 10 <3 4> 3-E @07 2 ACB:8. 0:A8<0;L=0O ACB>G=0O 4>70 A>AB02;O5B 30 <3 8;8 0,5 <3/:3 <0AAK B5;0. @8<5=5=85 8=J5:F8>==KE D>@< 4>;6=> ?@>8AE>48BL 2 B5G5=85 :0: <>6=> 1>;55 :>@>B:>3> ?@> <56CB:0 2@5<5=8 A :0: <>6=> 1>;55 1KAB@K< ?5@5E>4>< =0 ?@8<5=5=85 ?5@>@0;L=KE 8;8 @5:B0;L=KE D>@< <5B>;;>?@0<840. 5BO @8 ?@8<5=5=88 4;O ?@54>B2@0I5=8O ?>A;5>?5@0F8>==>9 B>H=>BK 8 @2>BK <5B>;;>?@0<84 A;54C5B ?@8<5=OBL ?>A;5 >:=G0=8O >?5@0F88. 5:><5=4C5<0O 4>70 <5B>;;>?@0<840 A>AB02;O5B 0,1-0,15 <3/:3 <0AAK B5;0 4> 3 @07 2 ACB:8. 0:A8 <0;L=0O ACB>G=0O 4>70 A>AB02;O5B 0,5 <3/:3 <0AAK B5;0. A;8 =5>1E>48<> ?@>4>;68BL ?@8 <5=5=85 ?@5?0@0B0, A;54C5B A>1;N40BL =5<5=55 G5< 6-G0A>2K5 8=B5@20;K. !E5<0 4>78@>20=8O.

>7@0AB, 3>4K	0A0 B5;0, :3	07>20O 4>70, <3	'0AB>B0
1-3	10-14	1	> 3 @07 2 ACB:8
3-5	15-19	2	> 3 @07 2 ACB:8
5-9	20-29	2,5	> 3 @07 2 ACB:8
9-18	30-60	5	> 3 @07 2 ACB:8
15-18	>60	10	> 3 @07 2 ACB:8

0:A8<0;L=0O ?@>4>;68B5;L=>ABL ?@8<5=5=8O <5B>;;>?@0<840 4;O ;5G5=8O CAB0=>2;5==>9 ?>A;5>?5@0F8>==>9 B>H=>BK 8 @2>BK A>AB02;O5B 48 G0A>2. 0:A8<0;L=0O ?@>4>;68B5;L=>ABL ?@8<5=5=8O <5B>;;>?@0<840 4;O ?@54>B2@0I5=8O >BA@>G5==>9 B>H=>BK 8 @2>BK, 2K720==KE E8<8>B5@0?859, A>AB02;O5B 5 ACB>:. 0F85=B0< A =0@CH5=85< DC=:F88 ?>G5: # 1>;L=KE A B5@<8=0;L=>9 AB04859 =0@CH5=8O DC=:F88 ?>G5: (:;8@5=A :@50B8=8=0 ≤15 <;/<8=) 4>7C <5B>;;>?@0<840 =5>1E>48<> C<5=LH8BL =0 75%. # 1>;L=KE A C<5@5==K< 8 BO65;K< =0@CH5=85< DC=:F88 ?>G5: (:;8@5=A :@50B8=8=0 15-60 <;/<8=) 4>7C <5B>;;>?@0<840 =5>1E>48<> C<5=LH8BL =0 50%.

0F85=B0< A ?5G5=>G=>9 =54>AB0B>G=>ABLN 2A;54AB285 C25;8G5=8O ?5@8>40 ?>;C2K2545=8O
?@8<5=OBL ?>;>28==CN 4>7C.

0F85=BK ?>68;>3> 2>7@0AB0.

!;54C5B @0AA<>B@5BL 2>7<>6=>ABL A=865=8O 4>7K C 1>;L=KE ?>68;>3> 2>7@0AB0 2A;54AB285
A=865=8O DC=:F88 ?>G5: 8 ?5G5=8, >1CA;>2;5==KE 2>7@0AB>

@>4>;68B5;L=>ABL ;5G5=8O.

F5;OE A2545=8O : <8=82 ?>1>G=KE @50:F89 A> AB>@>=K =5@2=>9 A8AB5I>G=KE @50:F89

?@5?0@0B A;54C5B ?@8<5=OBL B>;L:> 4;O :@0B:>2@5<5==>3> ;5G5=8O (4> 5 ACB>:).

>1>G=K5 @50:F88.

!> AB>@>=K A8AB528 8 ;89 A8AB5 <5B35<>3;>18=5<8O, :>B>@0O <>65B 1KBL A2O70=0 A 45D8F8B<
-F8B>E@>-@54C:B07K, >A>15==> C <;045=F52, AC;LD35<>3;>18=5<8O, :>B>@0O A2O70=0, 3;02=K<
>1@07><, A A>?CBAB2CNI8< ?@8<5=5=85< 28A>;8E 4>7 ?@5?0@0B>2, :>B>@K5 2KA2>1>640NB
A5@C.

!> AB>@>=K A5@45G=>-A>AC48AB>9 A8AB5 1@048:0@48O, >A>15==> ?@8 2=CB@825==>< ?@8
<5=5=88, >AB0=>2:0 A5@4F0 2 B5G5=85 :>@>B:>3> 2@5<5=8 ?>A;5 8=J5:F88, :>B>@0O <>65B 1KBL
A;54AB285< 1@048:0@488, 0@B8>25=B@8:C;O@=0O 1;>:040, 1;>:040 A8=CA>2>3> C7;0, >A>15==>
?@8 2=CB@825==>< ?@8<5=5=88, ?@>;>=30F8O 8=B5@20;0 QT, 65;C4>G:>200 B0E8:0@48O B8?0
«?8@CMB», 0@B5@80;L=0O 38?>B5=78O, H>:, >1<>@>:8 ?@8 2=CB@825==>< 22545=88, >AB@0O
0@B5@80;L=0O 38?5@B5=78O C ?0F85=B>2 A D5>E@><>F8B><>9.

0@538AB@8@>20=> >B45;L=K5 A>>1I5=8O > 2>7<>6=>AB8 @0728B8O B065;KE A5@45G=>-
A>AC48ABKE @50:F89, >1CA;>2;5==KE ?@8<5=5=85< <5B>;:>?@0<840, >A>15==> ?@8 2=CB@825==>
< 22545=88.

!> AB>@>=K =5@2=>9 A8AB5

M:AB@0?8@0<84=K5 @50:F88, :0: ?@028;>, 48AB>=88 (2 B>< G8A;5 >G5=L @54:> A;CG08
48A:8=5B8G5A:>3> A8=4@><0), >A>15==> C 45B59 8 ?0F85=B>2 2 2>7@0AB5 4> 30 ;5B, @8A:
:>B>@KE C25;8G8205BAO ?@8 ?@52KH5=88 ACB>G=>9 4>7K 0,5 <3/:3 <0AAK B5;0: A?07<
:C;>38@=K5 :@87K, =55AB5AB25==K5 ?>;>65=8O 3>;>2K 8 ?;5G, >?8AB>B>=CA, =CA;
?0@:8=A>=87< (B@5<>@, ?>45@3820=8O ABL

?>74=OO 48A:8=578O, :>B>@0O <>65B 1KBL =5>1@0B8<>9, <>65B 2>7=8:0BL ?@8 4;8B5;L=>9
B5@0?88 <5B>;:>?@0<84><, 2 >A>=2>=>< C ?>68;KE ?0F85=B>2 (>A>15==> 65=I8=), C ?0F85=B>2
A A0E0@=K< 48015B>< 8 >1KG=> @0728205BAO ?>A;5 >B<5=K ?@5?0@0B0. @>O2;O5BAO
=5?@>872>;L=K<8 42865=8O<8 O7K:0, ;8F0, @B0, G5;NAB8, 8=>340 =5?@>872>;L=K<8
42865=8O<8 BC;>28I0 8/8;8 :>=5G=>AB59;

=59@>;5?B8G5A:89 7;>:0G5AB25==K9 A8=4@><, 2;;NG0NI89 38?5@?8@5:A8N, 87<5=5==>5
A>7=0=85, ABL, @0AAB@>9AB2> DC=:F89 2535B0B82=>9 =5@2=>9 A8AB52KH5==K9
C@>25=L :@50B8=D>AD>:8=07K 2 AK2>@>B:5 :@>28. -B>B A8=4@>< O2;O5BAO
?>B5=F80;L=> ;5B0;L=K<, ?@8 53> 2>7=8=>25=88 A;54C5B =5<54;5==> ?@5:@0B8BL ?@85<
<5B>;:>?@0<840 8 A@>G=> =0G0BL ;5G5=85 (40=B@>;5=, 1@><>:@8?B8=);

3>;>2=0O 1>;L; 3>;>2>:@C65=85; A>;82>ABL; GC2AB2> CAB0;>AB8; GC2AB2> AB@0E0;
15A?>:>9AB2>; @0AB5@O==>ABL; HC< 2 CH0E.

"0:65 ACI5AB2C5B @8A: >AB@0E (:@0B:>2@5<5==KE) =52@>;>38G5A:8E @0AAB@>9AB2, :>B>@K9
28I5 C 45B59.

A8E8G5A:85 @0AAB@>9AB20: 45?@5AA8O, 30;;NF8=0F88, A?CB0==>ABL A>7=0=8O, B@52>6=>ABL,
15A?>:>9AB2>.

!> AB>@>=K ?8I520@8B5;L=>3> B@0:B0: B>H=>B0, 48A?5?A8O, ACE>ABL 2> @BC, 70?>@. @8 ?@8
<5=5=88 <5B>;:>?@0<840 2 4>70E, ?@52KH0NI8E ACB>G=CN C 1>;L=KE <>65B 2>7=8:0BL 480@5O.

!> AB>@>=K 8<9 A8AB568 8 ?>4:>6=>9 .;5BG0B:8: @50:F88 38?5@GC2AB28B5;L=>AB8, 2 B><
G8A;5: :>6=0O AK?L, 38?5@5<8O 8 7C4 :>68, :@0?82=8F0, >B5: 28=:5, 0=0D8;0:B8G5A:85 @50:F88,
2;;NG0O 0=0D8;0:B8G5A:89 H>:. 7-70 =0;8G8O 2 ;5:0@AB25==>9 D>@<5 =0B@8O AC;LD8B0 <>3CB
=01;N40BLAO >B45;L=K5 A;CG08 @50:F89 ?>2KH5==>9 GC2AB28B5;L=>AB8, >A>15==> C 1>;L=KE
1@>=E80;L=>9 0AB<>9, 2 2845 B>H=>BK, @2>BK, A28ABOI53> 4KE0=8O, >AB@>3> ?@8ABC?0 0ABO
A>7=0=8O 8;8 H>:0. -B8 @50:F88 <>3CB 8<5BL 8=48284C0;L=>5 B5G5=85.

!> AB>@>=K @5?@>4C:B82=>9 A8AB5 ?>A;5 1>;55 4;8B5;L=>9 B5@0?88 ?@5?0@0B><, 2 A2O78 A> AB820=85< A5:@5F88 ?@>;0:B8=0 <>3CB 2>7=8:0BL 38?5@?@>;0:B8=5<8O, 38=5:><0AB8O, 30;0:B>@5O 8;8=0@CH5=85 <5=AB@C0;L=>3> F8;;0, 0<5=>@5O; ?@8 @0728B88 MB8E O2;5=89 ?@8 <5=5=85 <5B>;>?@0<840 A;54C5B ?@5:@0B8BL.

01>@0B>@=K5 8AA;54>20=8O: ?>2KH5=85 C@>2=O M=78<>2 ?5G5=8.

1I85 @0AAB@>9AB20: 0AB5=8O, ?>2KH5==0O CB><;O5<>ABL.

?>4@>AB:>2 8 1>;L=KE A BO65;K<8=0@CH5=8O<8 DC=:F88 ?>G5: (?>G5G=0O =54>AB0B>G=>ABL), 2 @57C;LB0B5 :>B>@KE 70<54;O5BAO 2K2545=85 <5B>;>?@0<840, >A>15==> 2=8<0B5;L=> A;54OB 70 @0728B85< ?>1>G=KE O2;5=89. A;CG05 8E 2>7=8:=>25=8O ?@8<5=5=85 ?@5?0@0B0 A@07C 65 ?@5:@0B8BL.

8A: @0728B8O ?>1>G=KE @50:F89 A> AB>@>=K =5@2=>9 A8AB57@0AB05B ?@8 ?@8<5=5=88 ?@5?0@0B0 2 2KA>;8E 4>70E 8 ?@8 4;8B5;L=>< ?@8<5=5=88.

5@54>78@>2:0.

!8 A>;82>ABL, ?>=865=85 C@>2=O A>7=0=8O, A?CB0==>ABL A>7=0=8O, @074@068B5;L=>ABL, 15A?>:>9AB2> 8 53> CA8;5=85, AC4>@>38, M:AB@0?8@0<84=>-@=K5 @0AAB@>9AB20, =0@CH5=8O DC=:F88 A5@45G=>-A>AC48AB>9 A8AB52KH5=85< 8;8 ?>=865=85< 0@B5@80;L=>3> 402;5=8O, 30;;NF8=0F88, >AB0=>2:0 4KE0=8O 8 A5@45G=>9 45OB5;L=>AB8, 48AB>=8G5A:85 @50:F88. !>>1I0;>AL >1 548=8G=KE A;CG0OE <5B35<>3;>18=5<88.

5G5=85: M:AB@0?8@0<84=K5 @0AAB@>9AB20 CAB@0=ONB <54;5==K< 22545=85< 0=B84>B0 18?5@845=0. A;CG05 ?@8<5=5=8O 1>;LH8E 4>7 <5B>;>?@0<840 53> =5>1E>48<> C40;8BL 87 65;C4>G=>-:8H5G=>3> B@0:B0 ?CB5< ?@>20==K9 C3>;L 8 AC;LD0B =0B@8O. 0 687=5==> 206=K<8 DC=:F8O<8 >@30=87<0 =01;N40NB 4> ?>;=>3> 8AG57=>25=8O A8<>2 >B@02;5=8O.

@8<5=5=85 2 ?5@8>4 15@5<5==>AB8 8;8 :>@<;5=8O 3@C4LN.

5@5<5==>ABL.

>;LH>5 :>;8G5AB2> 40==KE, ?>;CG5==KE A CG0AB85< 15@5<5==KE 65=I8= (1>;55 1000 @57C;LB0B>2 A ?@8<5=5=85< ?@5?0@0B0), C:07K205B=0 >BACBAB285 B>:A8G=>AB8, :>B>@0O ?@82>48B : <0;LD>@<0F8O< 8;8 D5B>B>:A8G=>AB8. 5B>;>?@0<84 <>6=> ?@8<5=OBL 2> 2@5 >@<;5=85 3@C4LN.

5B>;>?@0<84 2 =57=0G8B5;L=>< :>;8G5AB25 ?@>=8:05B 2 3@C4=>5 <>;>:. >MB>5=4C5BAO ?@8 <5=OBL <5B>;>?@0<84 2> 2@5@<;5=8O 3@C4LN. 5>1E>48<> @0AA<>B@5BL 2>7<>6=>ABL >B<5=K <5B>;>?@0<840 C 65=I8=, :>B>@K5 :>@

5B8.

5B>;>?@0<84 ?@>B82>?>:070= 45BO< 4> 1 3>40.

A>15==>AB8 ?@8<5=5=8O.

52@>;>38G5A:85 =0@CH5=8O.

>3CB =01;N40BLAO M:AB@0?8@0<84=K5 =0@CH5=8O, >A>15==> C 45B59, 8/8;8 ?@8 ?@8<5=5=88 2KA>;8E 4>7. -B8 @50:F88 >1KG=> =01;N40NBAO 2 =0G0;5 ;5G5=8O 8 <>3CB 2>7=8:0BL ?>A;5 >4=>:@0B=>3> ?@8<5=5=8O. A;CG05 @0728B8O M:AB@0?8@0<84=KE A8<>2 <5B>;>?@0<84 =C6=> =5<54;5==> >B<5=8BL. >1I5< MB8 MDD5:BK ?>A;5 ?@5:@0I5=8O ;5G5=8O ?>;=>ABLN 8AG570NB, => <>3CB B@51>20BL A8<0B8G5A:>3> ;5G5=8O (15=7>48075?8=K C 45B59 8/8;8 0=B8E>;8=5@38G5A:85 ?@>B82>?0@:8=A>=8G5A:85 ;5:0@AB25==K5 A@54AB20 C 27@>A;KE).

564C :064K< 22545=85< <5B>;>?@0<840, 4065 2 A;CG05 @2>BK 8 >BB>@65=8O 4>7K, GB>1K 871560BL ?5@54>78@>2:8, =5>1E>48<> A>1;N40BL :0: <8=8

@8 ?@8<5=5=88 <5B>;>?@0<840 2 A>G5B0=88 A =59@>;5?B8:0<8, 0 B0:65 ?@8 <>=>B5@0?88 <5B>;>?@0<84>< A>>1I0;>AL > @0728B88 7>;:0G5AB25==>3> =59@>;5?B8G5A:>3> A8=4@<0. A;CG05 2>7=8:=>25=8O A8<>2 7>;:0G5AB25==>3> =59@>;5?B8G5A:>3> A8=4@<0 ?@8<5=5=8O <5B>;>?@0<840 =5>1E>48<> =5<54;5==> ?@5:@0B8BL 8 =0G0BL A>>B25BAB2CNI55 ;5G5=85.

?0F85=B>2 A A>?CBAB2CNI8<8 =52@>;>38G5A:8<8 701>;520=8O<8 8 C ?0F85=B>2, ?>;CG0NI8E ;5G5=85 4@C38<8 ;5:0@AB25==K<8 ?@5?0@0B0<8, 459AB2CNI8<8 =0 F5=B@0;L=CN =5@2=CN A8AB51E>48<> 1KBL >A>15==> >AB>@>6=K<8.

@8 ?@8<5=5=88 <5B>;>?@0<840 <>3CB B0:65 CA8;820BLAO A8;57=8 0@:8=A>=0.

5B35<>3;>18=5<8O.

!>>1I0;>AL > A;CG0OE <5B35<>3;>18=5<88, :>B>@K5 <>3CB 1KBL A2O70=K A 45D8F8B× NADH-F8B>E@>

!5@45G=K5 @0AAB@>9AB20.

!>>1I0;>AL > BO65;KE ?>1>G=KE @50:F8OE A> AB>@>=K A5@45G=>-A>AC48AB>9 A8AB5AB@>9 A>AC48AB>9 =54>AB0B>G=>AB8, BO65;>9 1@048:0@488, >AB0=>2:8 A5@4F0 8 C4;8=5=85 8=B5@20;0 QT, :>B>@K5 =01;N40;8AL ?>A;5 ?@85<0 <5B>;;>?@0<840 2 D>@<5 8=J5:F89, >A>15==> ?>A;5 22545=8O.

=CB@825==> ?@5?0@0B A;54C5B 22>48BL ?CB5< <54;5==>9 1>;NA=>9 8=J5:F88 (<8=8

0@CH5=85 DC=:F88 ?>G5: 8 ?5G5=8.

0F85=B0< A =0@CH5=85< DC=:F88 ?>G5: 8;8 BO65;K< =0@CH5=85< DC=:F88 ?5G5=8 @5:> <5=4C5BAO C<5=LH5=85 4>7K.

!;54C5B A >AB>@>6=>ABLN ?@8<5=OBL ?@5?0@0B C ?0F85=B>2 3@C?? @8A:0, 0 8<5==> C ?0F85=B>2 ?>68;>3> 2>7@0AB0 A @0AAB@>9AB20<8 A5@45G=>9 ?@>2>48<>AB8, A =5A:>@>5:B8@>20==K< 48A10;0=A>< M;5:B@>;8B>2 8;8 1@048:0@4859, 8 ?0F85=B>2, ?@8=8<0NI8E 4@C385 ?@5?0@0BK, :>B>@K5 C4;8=ONB 8=B5@20; QT. @5?0@0B =5 A;54C5B ?@8<5=OBL 4;O ;5G5=8O E@>=8G5A:8E 701>;520=89, B0:8E :0: 30AB@>?0@57, 48A?5?A8O 8 30AB@>M7>D0350;L=0O @5D;N:A=0O 1>;57=L 8;8 :0: 4>?>;=8B5;L=>5 A@54AB2> ?@8 ?@>2545=88 E8@C@38G5A:8E 8;8 @048>;>38G5A:8E ?@>F54C@.

!>>A>1=>ABL 2;8OBL =0 A:>@>ABL @50:F88 ?@8 C?@02;5=88 02B>B@0=A?>@B× 8;8 @01>B5 A 4@C38<8 <5E0=87<0<8.

@8 ?@8<5=5=88 ?@5?0@0B0 A;54C5B 2>745@60BLAO >B ?>B5=F80;L=> >?0A=KE 284>2 45OB5;L=>AB8, B@51CN18E ?>2KH5==>3> 2=8<0=8O (C?@02;5=85 02B>B@0=A?>@B><, @01>B0 A 4@C38<8 <5E0=87<0<8).

708<>459AB285 A 4@C38<8 ;5:0@AB25==K<8 A@54AB20<8 8 4@C385 284K 2708<>459AB289.

@>B82>?>:070==K5 :><18=0F88.

52>4>?0 8;8 4>?0<8=5@38G5A:85 03>=8ABK 8 <5B>;;>?@0<84 E0@0:B5@87CNBAO 2708<=K< 0=B03>=87<>

><18=0F88, :>B>@KE A;54C5B 871530BL.

;>3>;L CA8;8205B A540B82=>5 459AB285 <5B>;;>?@0<840.

><18=0F88, =0 :>B>@K5 A;54C5B >1@0B8BL 2=8<0=85.

@8 >4=>2@5<5==>< ?@8<5=5=88 A ?5@>@0;L=K<8 ;5:0@AB25==K<8 A@54AB20<8, =0?@8<5@ ?0@0F5B0<>;<, <5B>;;>?@0<84 <>65B 2;8OBL =0 8E 01A>@1F8N 2 @57C;LB0B5 2>7459AB28O =0 <>B>@8:C 65;C4:0.

=B8E>;8=5@38G5A:85 A@54AB20 8 ?@>872>4=K5 <>@D8=0: 0=B8E>;8=5@38G5A:85 A@54AB20 8 ?@>872>4=K5 <>@D8=0 E0@0:B5@87CNBAO 2708<=K< 0=B03>=87<>< A <5B>;;>?@0<84>< >B=>A8B5;L=> 2;8O=8O =0 <>B>@=CN 0:B82=>ABL ?8I520@8B5;L=>3> B@0:B0.

=3818B>@K F5=B@0;L=>9 =5@2=>9 A8AB5872>4=K5 <>@D8=0, =59@>;5?B8:8, A540B82=K5 0=B838AB0<8==K5-1;>:0B>@K @5F5?B>@>2 H₁, A540B82=K5 0=B845?@5AA0=BK, 10@18BC@0BK, :;>=848= 8 @>4AB25==K5 ?@5?0@0BK): ?>B5=F8@CNB 459AB285 <5B>;;>?@0<840.

59@>;5?B8:8: ?@8 ?@8<5=5=88 <5B>;;>?@0<840 2 :><18=0F88 A 4@C38<8 =59@>;5?B8:0<8 <>65B 2>7=8:0BL :CO2;5=85 M:AB@0?8@0<84=KE @0AAB@>9AB2.

!5@>B>=8=5@38G5A:85 ?@5?0@0BK: 8A?>;L7>20=85 <5B>;;>?@0<840 2 A>G5B0=88 A A5@>B>=8=5@38G5A:8<8 ?@5?0@0B0<8, =0?@8<5@, A5;5:B82=K<8 8=3818B>@0<8 >1@0B=>3> 70E20B0 A5@>B>=8=0 (!) <>65B ?>2KA8BL @8A: @0728B8O A5@>B>=8=>2>3> A8=4@>0. 83>:A8=: <5B>;;>?@0<84 <>65B C<5=LH0BL 18>4>ABC?=>ABL 483>:A8=0. 5>1E>48<> ?@>2>48BL BI0B5;L=K9 <>=8B>@8=3 :>=F5=B@0F88 483>:A8=0 2 ?;07<5 :@>28. ?>A?>@8=: <5B>;;>?@0<84 ?>2KH05B 18>4>ABC?=>ABL F8;>A?>@8=0 (Cmax =0 46% 8 2;8O=85 =0 22%). 5>1E>48<> ?@>2>48BL BI0B5;L=K9 <>=8B>@8=3 :>=F5=B@0F88 F8;>A?>@8=0 2 ?;07<5 :@>28. ;8=8G5A:85 ?>A;54AB28O MB>3> O2;5=8O >:>=G0B5;L=> =5 >?@545;5=K.

820:C@89 8 AC:A0<5B>=89: 8=J5:F8O <5B>;;>?@0<840 <>65B C25;8G8BL ?@>4>;68B5;L=>ABL =5@2=>-3> 1>;0 (2 A2O78 A C3=5B5=85< E>;8=MAB5@07K ?;0728).

>I=K5 8=3818B>@K CYP2D6: C@>2=8 M:A?>78F88 <5B>;>?@0<840 ?>2KH0NBAO ?@8 >4=>2@5
<5=>< 53> ?@8<5=5=88 A A8;L=K<8 8=3818B>@0<8 CYP2D6, =0?@8<5@, D;C>:A5B8=>< 8
?0@>:A5B8=>BO ;:8=8G5A:00 7=0G8<>ABL MB>3> B>G=> =58725AB=0, ?0F85=B>2 =5>1E>48<>
?@>2>48BL =01;N45=8O =0 ?@54<5B ?>1>G=KE @50:F89. 5B>;>?@0<84 <>65B ?@>4;8BL 459AB285
AC:F8=8;E>;8=0.

A2O78 A A>45@60=85< 2 8=J5:F8>==< @0AB2>@5 AC;LD8B0 =0B@8O, B80<8= (28B0<8= 1),
?@8=OBK9 >4=>2@5<5=> A <5B>;>?@0<84<, <>65B 1KAB@> @0AI5?;OBLAO 2 >@30=87<5.

\$0@<0>;>38G5A:85 A2>9AB20.

\$0@<0>: >48=0<8:0.

5B>;>?@0<84 O2;O5BAO F5=B@0;L=K< 4>?0<8=>2K< 0=B03>=8AB<, :>B>@K9 B0:65 >:07K205B
?5@8D5@8G5A:CN E>;8=5@38G5A:CN 0:B82=>ABL.

B<5G0NB 420 >A=>2=KE MDD5:B0 ?@5?0@0B0: ?@>B82>@2>B=K9 8 MDD5:B CA:>@5=8O
>?>@>6=5=8O 65;C4:0 8 ?@>E>645=8O A:2>7L B>=:CN :8H:C.

@>B82>@2>B=K9 MDD5:B 2K720= 459AB285< =0 F5=B@0;L=CN B>G:C AB2>;>2>9 G0AB8 <>730 (E5
<>@5F5?B>@K 0:B828@CNI00 7>=0 @2>B=>3> F5=B@0), 25@>OB=>, 87-70 B>@<>65=8O 4>?0
<8=5@38G5A:8E =59@>=>2.

#A8;5=85 ?5@8AB0;LB8:8 B0:65 G0AB8G=> :>=B@>;8@C5BAO 2KAH8<8 F5=B@0<8, => B0:65
G0AB8G=> <>65B 1KBL 70459AB2>20= <5E0=87< ?5@8D5@8G5A:>3> 459AB28O 2<5AB5 A
0:B820F859 ?>AB30=3;8>=0@=KE E>;8=5@38G5A:8E @5F5?B>@>2 8, 2>7<>6=>, C3=5B5=85< 4>?0
<8=5@38G5A:8E @5F5?B>@>2 65;C4:0 8 B>=:>9 :8H:8. '5@57 38?>B0;0@48=8@C5B 42830B5;L=CN
0:B82=>ABL 25@E=53> >B45;0 65;C4>G=>=:8H5G=>3> B@0:B0: ?>2KH05B B>=CA 65;C4:0 8 :8H5G=8:0,
CA:>@O5B >?>@>6=5=85 65;C4:0, C<5=LH05B 30AB@>AB07, ?@5?OBAB2C5B ?8;>@8G5A:>
D0350;L=>@<0;87C5B 2K45;5=85 65;G8, C<5=LH05B A?07< AD8=:B5@0 448, =5 87<5=OO 53> B>=CA,
CAB@0=O5B 48A:8=578N 65;G=>3> ?C7K@O.

>1>G=K5 MDD5:BK @0A?@>AB@0=ONBAO 3;02=K< >1@07>< =0 M:AB@0?8@0<84=K5 A8A=>25
:>B>@KE ;568B <5E0=87< 4>?0<8=-@5F5?B>@-1;>:8@CNI53> 459AB28O =0 F5=B@0;L=CN =5@2=CN
A8AB5

;8B5;L=>5 ;5G5=85 <5B>;>?@0<84<< <>65B 2K720BL @>AB :>=F5=B@0F88 ?@>;0:B8=0 2 AK2>@>B:5
:@>28 2A;54AB285 >BACBAB28O 4>?0<8=5@38G5A:>3> B>@<>65=8O A5:@5F88 ?@>;0:B8=0. #
65=I8= >?8A0=K A;CG08 30;0:B>@58 8 =0@CH5=8O <5=AB@C0;L=>3> F8;;0, C <0AB8O. 4=0:> MB8 A8
A;5 ?@5:@0I5=8O ;5G5=8O.

\$0@<0>: :8=5B8:0.

0G0;> 459AB28O =0 65;C4>G=>=:8H5G=K9 B@0:B >B<5G05BAO G5@57 1-3 <8=CBK ?>A;5
2=CB@825==>3> 22545=8O 8 G5@57 10-15 <8=CB ?>A;5 2=CB@83> 22545=8O. =B8M<5B8G5A:>5
459AB285 A>E@0=O5BAO 2 B5G5=85 12 G0A>2. ! 15;;0<8 ?;0728 A2O7K205BAO 13-30 % ?@5?0@0B0.
1J5< @0A?@545;5=8O 3,5 ;/:3. @>=8:05B G5@57 35<0B>M=F5D0;8G5A:89 8 ?;0F5=B0@=K9 10@L5@K,
2K45;O5BAO 2 3@C4=>5 <>;>: 5B01>;878@C5BAO 2 ?5G5=8. 5@8>4 ?>;C2K2545=8O 4-6 G0A>2.
'0ABL 4>7K (>:>;> 20 %) 2K2>48BAO 2 8AE>4=>9 D>@<5, 0 >AB0;L=>5 (>:>;> 80 %) ?>A;5
<5B01>;8G5A:8E ?@52@0I5=89 ?5G5=LN 2K2>48BAO ?>G:0<8 2 A>548=5=8OE A 3;N:C@>=>2>9 8;8
A5@=>9 :8A;>B>9.

\$0@<0F52B8G5A:85 E0@0:B5@8AB8:8.

A=>2=K5 D878:>-E8<8G5A:85 A2>9AB20: ?@>7@0G=0O 15AF25B=0O 684:>ABL.

5A>2<5AB8<>ABL.

=J5:F8>==K9 @0AB2>@ <5B>;>?@0<840 =5;L7O A<5H820BL A> I5;>G=K<8 8=DC78>==K<8
@0AB2>@0<8.

!@>: 3>4=>AB8. 4 3>40.

#A;>28O E@0=5=8O.

%@0=8BL 2 =54>ABC?=×< 4;O 45B59 <5AB5 2 >@838=0;L=>9 C?0:>2:5 ?@8 B5@06820BL.

#?0:>2:0.

> 2 <; 2 0 5 0=BC@=>9 OG59:>2>9 C?0:>2:5; ?> 1 8;8 ?> 2 :>=BC@=K5 OG59:>2K5 C?0:>2:8 2 ?0G:5; ?> 10 0=BC@=>9 OG59:>2>9 C?0:>2:5; ?> 1 :>=BC@=>9 OG59:>2>9 C?0:>2:5 2 ?0G:5; ?> 10 0@>1:5.

0B53>@8O >B?CA:0. > @5F5?BC.

@>872>48B5;L.

'«\$0@<0F52B8G5A:0O D8@<0 «0@=8F0».

5AB>=0E>645=85.

#: @08=0, 02093, 3. 852, C;.>@8A?>;LA:0O, 13.