

C,P° P±C-P»CHC€ C†PëC,PsC,PsPeC†PëC‡PSPsCĤ PIC-PrPSPsC†PSPs CĤC‡PrCř
P»C-PSC-PNë PiCřC...P»PëPSPSPëC... PeP»C-C,PëPS P»CĤPrPëPSPë C,P° PjPëC€PμPNë.
PμCĤPëPiPSC-C‡PμPSPSC‡ P”PќPљ-C,PsPiPsC-P·PsPjPμCĤP°P·Pë P† PiC-Pr PrC-C”CĤ
C-CĤPëPSPsC,PμPeP°PSCř C‡Pë SN-38 PiCĤPëP·PIPsPrPëC,CH PrPs
PiPsC€PePsPrP¶PμPSCĤ PsPrPSPsP»P°PSC†CĤPiPsPIPsC— P”PќPљ, C‡PeC-
P±P»PsPeCřCĤC,CH CĤPμPiP»C-PeP°C,PëPIPSCř PIPëP»PeCř P”PќPљ C,P°
PiCĤPëP·PIPsPrC‡C,CH PrPs C†PëC,PsC,PsPeC†PëC‡PSPsC— PrC-C—. P’CřP»Ps
PIC†C,P°PSPsPIP»PμPSPs, C°Ps C,P°PePëPNë C†PëC,PsC,PsPeC†PëC‡PSPëPNë
PμC,,PμPeC, C” P·P°P»PμP¶PSPëPj PIC-Pr C‡P°C†Cř C,P° C†PiPμC†PëC,,C-C‡PSPëPj
PrP»C‡ S-C,,P°P·Pë PeP»C-C,PëPSPSPsPiPs C†PëPeP»Cř.

PљCĤC-Pj PiCĤPsC,PëPiCřC...P»PëPSPSPsC— P°PeC,PëPIPSPsC†C,C-, PSP°PNëP±C-P»CHC€
P·PSP°C‡Cř°PsCĤ C,,P°CĤPjP°PePsP»PsPiC-C‡PSPsCĤ PrC-C”CĤ C-CĤPëPSPsC,PμPeP°PSCř
C” PiCĤPëPiPSC-C‡PμPSPSC‡ P°PeC,PëPIPSPsC†C,C-
P°C†PμC,PëP»C...PsP»C-PSPμC†C,PμCĤP°P·Pë.

PμP°C†C-C”PSC,Pë P·C- P·PSPëP¶PμPSPsCĤ P°PeC,PëPIPSC-C†C,CĤ UGT1A1.

PjCĤPëPrPëPSPPrPëC,,PsC†C,,P°C,-PiP»CĤPeCřCĤPsPSC-P»C,CĤP°PSC†C,,PμCĤP°P·P° 1Pĥ1
(UGT1A1) P±PμCĤPμ CřC‡P°C†C,CH Cř PjPμC,P°P±PsP»C-C‡PSC-PNë C-PSP°PeC,PëPIP°C†C-C—
SN-38, P°PeC,PëPIPSPsPiPs PjPμC,P°P±PsP»C-C,Cř C-CĤPëPSPsC,PμPeP°PSCř, P·
CřC,PIPsCĤPμPSPSC‡Pj PSPμP°PeC,PëPIPSPsPiPs SN-38-PiP»CĤPeCřCĤPsPSC-PrCř (SN-38G).
P”PμPS UGT1A1 C...P°CĤP°PeC,PμCĤPëP·CřC”C,CHC†C‡ PIPëC†PsPePëPj
PiPsP»C-PjPsCĤC,,C-P·PjPsPj, C°Ps P·P°P±PμP·PiPμC‡CřC” PSP°C‡PIPSC-C†C,CH
CĤC-P·PSPsPjP°PSC-C,PSPëC... PIP°CĤC-P°PSC,C-PI C-PSC,PμPSC†PëPIPSPsC†C,C-
PjPμC,P°P±PsP»C-P·PjCř Cř PiCĤCřPiC-. 1 PsC†PsP±P»PëPIPëPNë PIP°CĤC-P°PSC, PiPμPSP°
UGT1A1 PjC-C†C,PëC,CH PiPsP»C-PjPsCĤC,,PSCř PrC-P»C‡PSPeCř PI PrC-P»C‡PSC†C-
PiCĤPsPjPsC,PsCĤP°, C†PμPNë PIP°CĤC-P°PSC, PSPsC†PëC,CH PSP°P·PICř UGT1A1*28.
PŷP°PePëPNë PIP°CĤC-P°PSC,, P° C,P°PePsP¶ C-PSC€C- C†PiP°PrPePsPIC- PiPsCĤCřC€PμPSPSC‡
PμPeC†PiCĤPμC†C-C— UGT1A1 (C,P°PeC- C‡Pe C†PëPSPrCĤPsPj P-PëP»CHP±PμCĤP° P°P±Ps
C†PëPSPrCĤPsPj PљCĤPëPiP»PμCĤP°-Pќ°PNëC‡CĤP°) PiPsPIbĤ™ C‡P·CřCĤC,CH P·C-
P·PSPëP¶PμPSPsCĤ P°PeC,PëPIPSC-C†C,CĤ C†CHPsPiPs C,,PμCĤPjPμPSC,Cř.
P PμP·CřP»CHC,P°C,Pë PjPμC,P°P°PSP°P»C-P·Cř C†PIC-PrC‡P°C,CH, C°Ps PiP°C†C-C”PSC,Pë
C-P· C†PëPSPrCĤPsPjPsPj PљCĤPëPiP»PμCĤP°-Pќ°PNëC‡CĤP° (C,PëPi 1 C,P° 2) P°P±Ps
PiPsPjPsP·PëPiPsC,Pë P·P° P°P»PμP»PμPj UGT1A1*28 (C†PëPSPrCĤPsPj P-PëP»CHP±PμCĤP°)
PIC...PsPrC‡C,CH PrPs PiCĤCřPiPë PiC-PrPIPëC°PμPSPsPiPs CĤPëP·PëPeCř
PIPëPSPëPePSPμPSPSC‡ PiPμPjP°C,PsP»PsPiC-C‡PSPsC— C,PsPeC†PëC‡PSPsC†C,C- (III C,P° IV
C†C,CřPiPμPSC-PI) PiC-C†P»C‡ PIPiPμPrPμPSPSC‡ C†PμCĤPμPrPSC-C... P°P±Ps
PIPëC†PsPePëC... PrPsP· C-CĤPëPSPsC,PμPeP°PSCř (>150 PjPi/Pj²).
P’P·P°C”PjPsP·PIbĤ™ C‡P·PsPe PjC-P¶ PiPμPSPsC,PëPiPsPj UGT1A1 C,P°
PIPëPSPëPePSPμPSPSC‡Pj PrC-P°CĤPμC— PIPSP°C†P»C-PrPsPe PrC-C—
C-CĤPëPSPsC,PμPeP°PSCř PSPμ PIC†C,P°PSPsPIP»PμPSPs.

PμP°C†C-C”PSC,P°Pj P· B PIC-PrPsPjPëPjPë PiPsPjPsP·PëPiPsC,P°PjPë P·P° P°P»PμP»PμPj
UGT1A1*28 C†P»C-Pr P·P°C†C,PsC†PsPICřPIP°C,Pë P·PIPëC‡P°PNëPSCř PiPsC‡P°C,PePsPICř
PrPsP·Cř C-CĤPëPSPsC,PμPeP°PSCř. P’PsPrPSPsC‡P°C† P·P° C,P°PePëPjPë PiP°C†C-C”PSC,P°PjPë
C†P»C-Pr C†PiPsC†C,PμCĤC-PiP°C,Pë C°PsPrPs PiCĤPsC‡PIC-PI
PiPμPjP°C,PsP»PsPiC-C‡PSPsC— C,PsPeC†PëC‡PSPsC†C,C-. P”P»C‡ PiP°C†C-C”PSC,C-PI, Cř
C‡PePëC... PiC-Pr C‡P°C† PiPsPiPμCĤPμPrPSC-C... PeCřCĤC†C-PI P»C-PeCřPIP°PSPSC‡ PIP¶Pμ
PIPëPSPëPeP°P»Pë PiCĤPsC‡PIPë PiPμPjP°C,PsP»PsPiC-C‡PSPsC— C,PsPeC†PëC‡PSPsC†C,C-,
C†P»C-Pr CĤPsP·PiP»C‡PSCřC,Pë PjPsP¶P»PëPIC-C†C,CH P·PSPëP¶PμPSPSC‡

PiPsC†P°C,PePsPIPsC— PrPsP·Pë C-CHjPëPSPsC,PμPeP°PSCr. PÿPsC†PSCr PIPμP»PëC†PëPSCr P·PSPëP¶PμPSPSCl PìPsC†P°C,PePsPIPsC— PrPsP·Pë PrP»C†C-C" C†C-C" C— PiC†C†PìPë PìP°C†C-C" PSC,C-PI PSPμ PIC†C,P°PSPsPIP»CHjPIP°P»Pë. P'CrPrCH-C†PëC- PìPsPrP°P»CHC€C- P·PjC-PSPë PrPsP·C†PIP°PSPSCl C†P»C-Pr PìCHjPsPIPsPrPëC,Pë, PIPëC...PsPrC†C†Pë P· C,PsPiPs, C†Pë PìP°C†C-C" PSC, PìPμCHjPμPSPsC†PëC,CH P»C-PeC†PIP°PSPSCl (PrPëPI. CHjPsP·PrC-P»Pë B«PhC†PsP±P»PëPIPsC†C,C- P·P°C†C,PsC†C†PIP°PSPSClB» C,P° B«PÿPìPsC†C-P± P·P°C†C,PsC†C†PIP°PSPSCl C,P° PrPsP·PëB»). PkP° C†CHjPsPiPsPrPSC- PSPμPrPsC†C,P°C,PSCHjPs PeP»C-PSC-C†PSPëC... PrP°PSPëC... PrP»C† PIPëC†PSPsPIPeC† C°%PsPrPs PrPsC†C-P»CHjPSPsC†C,C- PiPμPSPsC,PëPìC†PIP°PSPSCl PìP°C†C-C" PSC,C-PI P·P° P°P»PμP»C†PjPë UGT1A1.

PαP°C†PjP°PePsPeC-PSPμC,PëPeP°.

PμC-C†P»C† PIPIPμPrPμPSPSCl C-CHjPëPSPsC,PμPeP°PSCr PI PrPsP·C- 100-750 PjPi/Pj² C€P»C†C...PsPj 30-C...PIPëP»PëPSPSPsC— PIPSCrC,CHjC-C€PSCHjPsPIPμPSPSPsC— C-PSC,,C†P·C-C— PePsP¶PSC- 3 C,PëP¶PSC- C†PìPsC†C,PμCHjC-PiP°C" C,CHC†C† PìPIPs- P°P±Ps C,CHjPëC,,P°P·PsPIP° PìP»P°P·PjPsPIP° PμP»C-PjC-PSP°C†C-C† C-CHjPëPSPsC,PμPeP°PSCr. PÿPμCHjPμPrPSC-PNë PìP»P°P·PjPsPIPëPNë PeP»C-CHjPμPSC† - 15 P»/PìPsPr/Pj², PsP±B†™ C" Pj CHjPsP·PìPsPrC-P»C† PI CHjC-PIPSPsPIP°P¶PSPsPjC† C†C,P°PSC- (Vss) - 157 P»/Pj² PìPsPIPμCHjC...PSC- C,C-P»P°. PÿPμCHjPμPrPSC-PNë PìPμCHjC-PsPr PSP°PìC-PIPIPëPIPμPrPμPSPSCl P· PìP»P°P·PjPë PeCHjPsPIC- PìC-Pr C†P°C† PìPμCHjC€PsC— C,,P°P·Pë C,CHjPëC,,P°P·PsPIPsC— PjPsPrPμP»C- C†C,P°PSPsPIPëPI 12 C...PI, PìC-Pr C†P°C† PrCHjC†PiPsC— C,,P°P·Pë B†" 2,5 PìPsPrPëPSPë, PìC-Pr C†P°C† C,CHjPμC,CHjPsC— C,,P°P·Pë B†" 14,2 PìPsPrPëPSPë. PμP»P°P·PjPsPIP° PμP»C-PjC-PSP°C†C-C† SN-38 P±C†P»P° PrPIPsC,,P°P·PsPIP° P·C- C†PμCHjPμPrPSC-Pj PeC-PSC†PμPIPëPj PìPμCHjC-PsPrPsPj PSP°PìC-PIPIPëPIPμPrPμPSPSCl 13,8 PìPsPrPëPSPë.

P—PIB†™ C†P·C†PIP°PSPSCl P· P±C-P»PeP°PjPë PìP»P°P·PjPë PeCHjPsPIC- C† PrPsC†P»C-PrP¶PμPSPSC- *in vitro* C†C,P°PSPsPIPëC,CH PìCHjPëP±P»PëP·PSPs 65 % PrP»C† C-CHjPëPSPsC,PμPeP°PSCr C- 95 % PrP»C† PjPμC,P°P±PsP»C-C,C† SN-38.

P'C-P»CHC€Pμ 50 % PrPsP·Pë C-CHjPëPSPsC,PμPeP°PSCr, PIPIPμPrPμPSPsPiPs PIPSCrC,CHjC-C€PSCHjPsPIPμPSPSPs, PIPëPrC-P»C†C" C,CHC†C† C† PSPμP·PjC-PSPμPSPsPjC† PIPëPiP»C†PrC-, 33 % PIPëPrC-P»C†C" C,CHC†C† P· PeP°P»PsPj, PI PsC†PSPsPIPSPsPjC† C†PμCHjPμP· P¶PsPIC±, C,P° 22 % B†" C-P· C†PμC†PμCH.

PμP»C-CHjPμPSC† C-CHjPëPSPsC,PμPeP°PSCr P·PjPμPSC€C†C" C,CHC†C† PjP°PNëP¶Pμ PSP° 40 % C† PìP°C†C-C" PSC,C-PI P· P±C-P»C-CHjC†P±C-PSPμPjC-C" CH (PePsPSC†PμPSC,CHjP°C†C-C† P·P°PìP°P»CHjPSPsPiPs P±C-P»C-CHjC†P±C-PSCr PI C†PëCHjPsPIP°C,C†C- PeCHjPsPIC- C† 1,5-3 CHjP°P·Pë PIPëC°%P° P·P° PIPμCHjC...PSC† PjPμP¶C† PSPsCHjPjPë). Pj C†PëC... PìP°C†C-C" PSC,C-PI PrPsP·P° C-CHjPëPSPsC,PμPeP°PSCr 200 PjPi/Pj² PìCHjPëP·PIPsPrPëC,CH PrPs PμPeC†PìPsP·PëC†C-C— PìCHjPμPìP°CHjP°C,C† PI PìP»P°P·PjC- PeCHjPsPIC-, C†PeP° PìPsCHjC-PIPSClPSPSP° P· C,P°PePsCH PìCHjPë PrPsP·C- 350 PjPi/Pj² C† C...PIPsCHjPëC... PSP° CHjP°Pe P· PSPsCHjPjP°P»CHjPSPëPjPë PìPsPeP°P·PSPëPeP°PjPë C,,C†PSPeC†C-C— PìPμC†C-PSPePë.

P†PSC,PμPSC†PëPIPSC-C†C,CH PSP°PNëP±C-P»CHC€ PIPëCHjP°P¶PμPSPëC... C,PsPeC†PëC†PSPëC... PμC,,PμPeC,C-PI C-CHjPëPSPsC,PμPeP°PSCr (PSP°PìCHjPëPeP»P°Pr, P»PμPNëPePsPSPμPNëC,CHjPsPìPμPSC-C— C- PrC-P°CHjPμC—) PìPsPIB†™ C†P·P°PSP° C-P· PIPìP»PëPIPsPj (PìP»PsC°%P° PìC-Pr PeCHjPëPIPsCH B«PePsPSC†PμPSC,CHjP°C†C-C†C-C†P°C†B» (AUC)) PSPμP·PjC-PSPμPSPsPiPs C-CHjPëPSPsC,PμPeP°PSCr C,P° PNëPsPiPs PjPμC,P°P±PsP»C-C,C† SN-38. P†C†C,PsC,PSPëPNë PIP·P°C" PjPsP·PIB†™ C†P·PsPe

СГРiPsCГC, PμCГC-PiP°PICГC PjC-P¶ PiPμPjP°C, PsP»PsPiC-C‡PSPsCГ
C, PsPeCГP€C‡PSC-CГC, CГ (P·PjPμPSC€PμPSPSC P€C-P»CHPePsCГC, C-
P»PμPN€PePsC‡P€C, C-PI C- PSPμPN€C, CГPsC„C-P»C-PI PrPs PjC-PSC-PjCГPjCГ) P°P±Ps
C-PSC, PμPSCГP€PIPC-CГC, CГ PrC-P°CГPμC— PN€ AUC C-CГP€PSPsC, PμPeP°PSCГ C, P°
PN€PsPiPs PjPμC, P°P±PsP»C-C, CГ SN-38 PiCГP€ PjPsPSPsC, PμCГP°PiC-C—.

PљP»C-PSC-C‡PSC- C...P°CГP°PeC, PμCГP€CГC, P€PeP€.

PμPsPeP°P·P°PSPSC¶.

P>C-PeCГPIP°PSPSC PIP°C‡C-C”PSC, C-PI C-P· PiPsC€P€CГPμPSP€Pj
PePsP»PsCГPμPeC, P°P»CHPSP€Pj CГP°PePsPj:

B· CГ PePsPjP±C-PSP°C‡C-C— P· 5-C„C, PsCГCГCГP°C‡P€P»PsPj (5-PαPJ) C, P°
C„PsP»C-PSC-C”PIPsCГ PeP€CГP»PsC, PsCГ (PαPљ), C¶PeC%Ps PiP°C‡C-C”PSC, P€ PSPμ
PsC, CГP€PjCГPIP°P»P€ PiPsPiPμCГPμPrPSCГPsC— C...C-PjC-PsC, PμCГP°PiC-C— PrP»C¶
P»C-PeCГPIP°PSPSC PIPsC€P€CГPμPSPsPiPs P·P°C...PIPsCГCГPIP°PSPSC;

B· C¶Pe PjPsPSPsC, PμCГP°PiC-C¶, C¶PeC%Ps PICГC, P°PSPsPIP»PμPSP€PN€ CГPμP¶P€Pj
P»C-PeCГPIP°PSPSC C-P· P·P°CГC, PsCГCГPIP°PSPSC Pj 5-PαPJ PIP€C¶PIP€PICГC¶
PSPμPμC„PμPeC, P€PIPCG.

P‡CГP€PSPsC, PμPeP°PS PhPjP°PeCГP° CГ PePsPjP±C-PSP°C‡C-C— P·
C‡PμC, CГPeCГP€PjP°P±PsPj PiPsPeP°P·P°PSP€PN€ PrP»C¶ P»C-PeCГPIP°PSPSC
PIP°C‡C-C”PSC, C-PI C-P· PjPμC, P°CГC, P°C, P€C‡PSP€Pj
PePsP»PsCГPμPeC, P°P»CHPSP€Pj CГP°PePsPj P· PrP€PeP€Pj C, P€PiPsPj PiPμPSP° KRAS,
C%Ps CГCГPiCГPsIPsPrP¶CГC”C, CHCГC¶ PiPsCГP€P»PμPSPsCГ PμPeCГPiCГPμCГC-C”CГ
CГPμC‡PμPiC, PsCГP° PμPiC-PrPμCГPjP°P»CHPSPsPiPs C„P°PeC, PsCГP° CГPsCГC, CГ (P P·PαP),
C¶PeC- CГP°PSC-C€Pμ PSPμ PsC, CГP€PjCГPIP°P»P€ C...C-PjC-PsC, PμCГP°PiC-CГ, P°P±Ps
PiC-CГP»C¶ PSPμPμC„PμPeC, P€PIPCG— C‡P€C, PsC, PsPeCГP€C‡PSPsC— C, PμCГP°PiC-C—,
C¶PeP° PIPeP»CГC‡P°P»P° C-CГP€PSPsC, PμPeP°PS.

Pj PePsPjP±C-PSP°C‡C-C— P· 5-PαPJ, PαPљ C, P° P±PμPIP°C‡P€P·CГPjP°P±PsPj
P‡CГP€PSPsC, PμPeP°PS PhPjP°PeCГP° P·P°CГC, PsCГPsPICГCГC, CH C¶Pe
C, PμCГP°PiC-CГ PiPμCГC€PsC— P»C-PSC-C— PIP°C‡C-C”PSC, P°Pj C-P·
PjPμC, P°CГC, P°C, P€C‡PSP€PjP€ PeP°CГC‡P€PSPsPjP°PjP€ C, PsPICГC, PsC— P°P±Ps
PiCГC¶PjPsC— PeP€C€PeP€.

Pj PePsPjP±C-PSP°C‡C-C— P· PeP°PiPμC‡P€C, P°P±C-PSPsPj (P· PrPsPrP°PIP°PSPSC Pj
P±PμPIP°C‡P€P·CГPjP°P±CГ P°P±Ps P±PμP· PSCHPsPiPs) P‡CГP€PSPsC, PμPeP°PS PhPjP°PeCГP°
P·P°CГC, PsCГPsPICГCГC, CH C¶Pe C, PμCГP°PiC-CГ PiPμCГC€PsC— P»C-PSC-C—
PIP°C‡C-C”PSC, P°Pj C-P· PjPμC, P°CГC, P°C, P€C‡PSP€Pj PePsP»PsCГPμPeC, P°P»CHPSP€Pj
CГP°PePsPj.

PμCГPsC, P€PiPsPeP°P·P°PSPSC¶.

P-PëPIC- P°C,PμPSCrPNεPsPIP°PSC- PIP°PeC†PëPSPë (PSP°PïCḡPëPeP»P°Pr, PIP°PeC†PëPSP°PïCḡPsC,Pë P¶PsPIC,PSc— PiP°CḡCḡC†PePë) вḡ“ CḡPëP·PëPe PIPëPSPëPePSPμPSPSCḡCḡPëCḡC,PμPjPSPëC... P·P°C...PIPScḡCḡPIP°PSCḡ P· PjPsP¶P»PëPIPëPj P»PμC,P°P»CḡPSPëPj PSP°CḡP»C-PrPePsPj (PSP°PïCḡPëPeP»P°Pr, C-PSC,,PμPeC†C-C—). P¡PμPNε CḡPëP·PëPe P·P±C-P»CḡCḡCrC”C,CḡCḡCḡ, CḡPeC%oPs Cr PïP°C†C-C”PSC,C-PI CrP¶Pu

PiC7PëPiPSC-C#PµPSP° C-PjCfPSPSP° C7PëC7C,PµPjP° PIPSP°C7P»C-PrPsPe
PsC7PSPsPIPSPsPiPs P·P°C...PIPsC7C7PIP°PSPSC7. PhPrPSPsC#P°C7PSPµ
P·P°C7C,PsC7C7PIP°PSPSC7 P¶PëPIPëC... P°C,PµPSC7PNsPsPIP°PSPëC... PIP°PeC7PëPS
PiC7PsC,PëPiPsPeP°P·P°PSPs PiC-Pr C#P°C7 P»C-PeC7PIP°PSPSC7 C-C7PëPSPsC,PµPeP°PSPsPj
C,P° PiC7PsC,C7PiPsPj CëPµC7C,Pë PjC-C7C7C7C-PI PiC-C7P»C7 P·P°PeC-PSC#PµPSPSC7
C...C-PjC-PsC,PµC7P°PiC-C—. PÿP»C-Pr P·P°C7C,PsC7PsPIC7PIP°C,Pë
C-PSP°PeC,PëPIPsPIP°PSC- PIP°PeC7PëPSPë, C7PeC%Ps PIPsPSPë C-C7PSC7C7C,CH
(PiPsP»C-PsPjC-C”P»C-C,), P°P»Pµ PIC-PrPiPsPIC-PrCH PSP° C,P°PeC- PIP°PeC7PëPSPë
PjPsP¶Pµ P±C7C,Pë P·PSPëP¶PµPSP°.

P»C-PeP°C7C7CHPeC- P·P°C7PsP±Pë, PsPrPSPsC#P°C7PSPµ PiC7PëP·PSP°C#PµPSPSC7
C7PePëC... C-P· PiC7PµPiP°C7P°C,PsPj P7C7PëPSPsC,PµPeP°PS PhPjP°PeC7P° PSPµ
C7PµPePsPjPµPSPPrPsPIP°PSPs (PrPëPI. C7PsP·PrC-P» B«PhC7PsP±P»PëPIPsC7C,C-
P·P°C7C,PsC7C7PIP°PSPSC7B»):

PÿP»C-Pr C7PSPëPeP°C,Pë PsPrPSPsC#P°C7PSPsPiPs P·P°C7C,PsC7C7PIP°PSPSC7
C-C7PëPSPsC,PµPeP°PSC7 C,P° C7PëP»CHPSPëC...
C-PSP7C7PeC,PsC7C-PI/C-PSPiC-P±C-C,PsC7C-PI C7PëC,PsC...C7PsPjC7 P450 3A4
(CYP3A4), PsC7PeC-P»CHPePë C7Pµ PjPsP¶Pµ PiC7PëP·PIPsPrPëC,Pë PrPs P·PjC-PS
PjPµC,P°P±PsP»C-P·PjC7 C-C7PëPSPsC,PµPeP°PSC7 (PrPëPI. C7PsP·PrC-P»
B«PhC7PsP±P»PëPIPsC7C,C- P·P°C7C,PsC7C7PIP°PSPSC7B»).

PÿPëP»CHPSC- C-PSP7C7PeC,PsC7Pë CYP3A4 C,P°/P°P±Ps UGT1A1
(PSP°PiC7PëPeP»P°Pr, C7PëC,,P°PjPiC-C7PëPS, PeP°C7P±P°PjP°P·PµPiC-PS,
C,,PµPSPsP±P°C7P±C-C,P°P», C,,PµPSC-C,PsC—PS P°P±Ps P°PiP°P»C7C,P°PjC-Pr) B7“
C7PµP·C7P»CHC,P°C,Pë PrPµPeC-P»CHPePsC... PrPsC7P»C-PrP¶PµPSC7
PiC7PsPrPµPjPsPSC7C,C7C7PIP°P»Pë, C%Ps PsPrPSPsC#P°C7PSPµ
P·P°C7C,PsC7C7PIP°PSPSC7 PiC7PsC,PëC7C7PrPsPjPSPëC... PiC7PµPiP°C7P°C,C-PI,
C-PSP7C7PeC,PsC7C-PI CYP3A4 (PeP°C7P±P°PjP°P·PµPiC-PS,
C,,PµPSPsP±P°C7P±C-C,P°P» P°P±Ps C,,PµPSC-C,PsC—PS), PiC7PëP·PIPsPrPëC,CH PrPs
P·PjPµPSCëPµPSPSC7 PµC,,PµPeC,PëPIPsPSC7C,C- C-C7PëPSPsC,PµPeP°PSC7, SN-38
C,P° SN-38-PiP»CHPeC7C7PsPSC-PrC7, C%Ps, C7 C7PIPsC7 C#PµC7PiC7,
PiC7PëP·PIPsPrPëC,CH PrPs P·PjPµPSCëPµPSPSC7
C,,P°C7PjP°PePsPrPëPSP°PjC-C#PSPsPiPs PµC,,PµPeC,C7. P”C-C7 C,P°PePëC...
PiC7PsC,PëC7C7PrPsPjPSPëC... PiC7PµPiP°C7P°C,C-PI PiPsP»C7PiP°P»P° C7
P·PSPëP¶PµPSPSC- AUC PrP»C7 SN-38 C,P° SN-38-PiP»CHPeC7C7PsPSC-PrC7 PSP° 50 %
C#Pë PSP°PIC-C,CH P±C-P»CHCëPµ. P7C7C-Pj C-PSP7C7PeC7C-C—
C7PëC,PsC...C7PsPjC7 P450 3A4, P·PSPëP¶PµPSPSC7 C7C-PIPsC7
PµPeC7PiPsP·PëC7C-C— C-C7PëPSPsC,PµPeP°PSC7 C,P° PNsPiPs
PjPµC,P°P±PsP»C-C,C-PI PjPsP¶Pµ P±C7C,Pë PsP±C7PjPsPIP»PµPSPµ C,P°PePsP¶
PiPsC7PëP»PµPSPsC7 PiP»CHPeC7C7PsPSC-P·P°C7C-C”C7 C,P° P±C-P»CHCë
C-PSC,PµPSC7PëPIPsPëPj PIPëPIPµPrPµPSPSC7Pj C-P· P¶PsPIC7C7.

P»PµPSC-C,PsC—PS B7“ C7PëP·PëPe P·P°PiPsC7C,C7PµPSPSC7 C7C7PrPsPj
PIPSP°C7P»C-PrPsPe P·PSPëP¶PµPSPSC7 C-PSC,PµPSC7PëPIPsPSC7C,C-
PiPsPiP»PëPSP°PSPSC7 C,,PµPSC-C,PsC—PSC7 C7 C,C7P°PIPsPjC7 C,C7P°PeC,C- PiC-Pr
PIPiP»PëPIPsPj C7PëC,PsC,PsPeC7PëC#PSPsPiPs PiC7PµPiP°C7P°C,C7.

PÿPëP»CHPSC- C-PSPiC-P±C-C,PsC7Pë CYP3A4 (PSP°PiC7PëPeP»P°Pr,

PePμC,PsPePsPSP°P·PsP», C-C,CTHP°PePsPSP°P·PsP», PIPsCTHPëPePsPSP°P·PsP»,
PïPsP·P°PePsPSP°P·PsP», C-PSPiC-P±C-C,PsCTHPë PïCTHPsC,PμP°P·Pë,
PeP»P°CTHPëC,CTHPsPjC-C†PëPS, PμCTHPëC,CTHPsPjC-C†PëPS, C,PμP»C-C,CTHPsPjC-C†PëPS)
БҒ“ Cр CTHPμP·CрP»CHC,P°C,C- PrPsCрP»C-PrP¶PμPSPSC¶ P±CрP»Ps
PICрC,P°PSPsPIP»PμPSPs, C%Ps PsPrPSPsC†P°CрPSPμ P·P°CрC,PsCрCрPIP°PSPSC¶
PePμC,PsPePsPSP°P·PsP»Cр PïCTHPëP·PIPPrPëP»Ps PrPs P·PSPëP¶PμPSPSC¶ AUC
PjPμC,P°P±PsP»C-C,Cр APC PSP° 87 %, P° AUC PjPμC,P°P±PsP»C-C,Cр SN-38
P·PSPëP¶CрPIP°P»P°CрCH PSP° 109 % PïPsCTHC-PIPSCTHPSPs C-P·
P·P°CрC,PsCрCрPIP°PSPSC¶Pj C-CTHPëPSPsC,PμPeP°PSCр C¶Pe
PjPsPSPsC,PμCTHP°PïC-C—.

P†PSPiC-P±C-C,PsCTHPë UGT1A1 (PSP°PïCTHPëPeP»P°Pr, P°C,P°P·P°PSP°PIC-CTH,
PePμC,PsPePsPSP°P·PsP», CTHPμPiPsCTHP°C„PμPSC-P±) БҒ“ CTHPëP·PëPe
PïC-PrPIPëC%PμPSPSC¶ CрPëCрC,PμPjPSPsC— PμPeCрPïPsP·PëC†C-C—
P°PeC,PëPIPSsPiPs PjPμC,P°P±PsP»C-C,Cр C-CTHPëPSPsC,PμPeP°PSCр БҒ“ SN-38.
P>C-PeP°CTHC¶Pj CрP»C-Pr PICHP°C...PsPICрPIP°C,Pë C†CH PjPsP¶P»PëPIC-CрC,CH
PïCTHPë PsPrPSPsC†P°CрPSPsPjCр PïCTHPëP·PSP°C†PμPSPSC- C†PëC... PrPIPsC...
PïCTHPμPïP°CTHP°C,C-PI.

P†PSC€C- C-PSPiC-P±C-C,PsCTHPë CYP3A4 (PSP°PïCTHPëPeP»P°Pr, PeCTHPëP·PsC,PëPSC-P±,
C-PrPμP»P°P»C-P·PëP±) БҒ“ CTHPëP·PëPe PïC-PrPIPëC%PμPSPSC¶ C,PsPeCрPëC†PSPsCрC,C-
C-CTHPëPSPsC,PμPeP°PSCр PIPSP°CрP»C-PrPsPe P·PSPëP¶PμPSPSC¶ PN₂PsPiPs
PjPμC,P°P±PsP»C-P·PjCр PïCTHPë PsPrPSPsC†P°CрPSPsPjCр P·P°CрC,PsCрCрPIP°PSPSC- P·
PeCTHPëP·PsC,PëPSC-P±PsPj P°P±Ps C-PrPμP°P»C-P·PëP±PsPj.

P>C-PeP°CTHCрCHPeC- P·P°CрPsP±Pë, C¶PeC- CTHP°P·PsPj C-P· PïCTHPμPïP°CTHP°C,PsPj
P†CTHPëPSPsC,PμPeP°PS PhPjP°PeCрP° CрP»C-Pr P·P°CрC,PsCрPsPICрPIP°C,Pë P·
PsP±PμCTHPμP¶PSC-CрC,CH:

PhPSC,P°PiPsPSC-CрC,Pë PIC-C,P°PjC-PSCр Pљ БҒ“ PïC-PrPIPëC%PμPSPëPN₂
CTHPëP·PëPe PIPëPSPëPePSPμPSPSC¶ PeCTHPsPiPsC,PμC† C- C,CTHPsPjP±PsP·C-PI Cр
PïP°C†C-C”PSC,C-PI C-P· PïCрC...P»PëPSPSPëPjPë P·P°C...PIPsCTHCPIP°PSPSC¶PjPë.
P—P° PSP°C¶PIPSsCрC,C- PïPsPeP°P·P°PSCH PrPs P·P°CрC,PsCрCрPIP°PSPSC¶
P°PSC,P°PiPsPSC-CрC,C-PI PIC-C,P°PjC-PSCр Pљ PSPμPsP±C...C-PrPSPs
C†P°CрC,C-C€Pμ, PSC-P¶ P·P°P·PIPëC†P°PN₂, PePsPSC,CTHPsP»CTHIP°C,Pë
PïPsPeP°P·PSPëPe PhC-P¶PSP°CTHPsPrPSPsPiPs PSPsCTHPjP°P»C-P·PsPIP°PSPsPiPs
PIC-PrPSPsC€PμPSPSC¶ (PљPќP’).

P†PjCрPSPsCрCрPïCTHPμCрP°PSC,Pë (PSP°PïCTHPëPeP»P°Pr, C†PëPeP»PsCрPïPsCTHPëPS,
C,P°PeCTHPsP»C-PjCрCр) БҒ“ CTHPëP·PëPe PSP°PrPjC-CTHPSPsPiPs PïCTHPëPiPSC-C†PμPSPSC¶
C-PjCрPSPSPsC— CрPëCрC,PμPjPë P· CTHPëP·PëPePsPj CTHPsP·PIPëC,PeCр
PïCTHPsP»C-C„PμCTHP°C†C-C— P»C-PjC„PsC†PëC,C-PI.

P’P»PsPeP°C,PsCTHPë PSPμPN₂CTHPsPjБҒ™ C¶P·PsPIPsC— PIP·P°C”PjPsPrC-C— БҒ“
PSPμPjPsP¶P»PëPIPs PIPëPeP»CTHC†PëC,Pë PIP·P°C”PjPsPrC-CTH PjC-P¶
C-CTHPëPSPsC,PμPeP°PSPsPj C,P° P±P»PsPeP°C,PsCTHP°PjPë PSPμPN₂CTHPsPjБҒ™ C¶P·PsPIPsC—
PIP·P°C”PjPsPrC-C—. PhCрPeC-P»CHPePë C-CTHPëPSPsC,PμPeP°PS C†PëPSPëC,CH
P°PSC,PëC...PsP»C-PSPμCрC,PμCTHP°P·PSCр PrC-CTH, PïCTHPμPïP°CTHP°C,Pë, C%Ps C,P°PePsP¶
C†PëPSC¶C,CH P°PSC,PëC...PsP»C-PSPμCрC,PμCTHP°P·PSCр PrC-CTH, PjPsP¶CрC,CH
P·P±C-P»CHC€CрPIP°C,Pë C,CTHPëPIP°P»C-CрC,CH PSPμPN₂CTHPsPjБҒ™ C¶P·PsPIPsPiPs

P±P»PsPeCíPíP°PSPSCİ ÇíCíPeCíP°PjPµC,PsPSC-Ç C,P° PíCĤPsC,PëPrC-ÇİC,Pë
PSPµPNëCĤPsPjBĤ™ ÇİP·PsPIPsPjCí P±P»PsPeCíPíP°PSPSCĤ
PSPµPrPµPíPsP»ÇİCĤPëP·CíCĤC±PëC... PíCĤPµPíP°CĤP°C,C-PI.

P†PSC€C- PePsPjP±C-PSP°C†C-C—.

5-PαPJ/PαPљ **БĤ**“ PsPrPSPsC±P°CíPSPµ P·P°CíC,PsCíCíPíP°PSPSCİ 5-PαPJ/PαPљ Çí
CíPeP»P°PrC- PePsPjP±C-PSPsPíP°PSPsC— C,PµCĤP°PíC-C— PSPµ P·PjC-PSCHC”
C„P°CĤPjP°PePsPeC-PSPµC,PëPeCí C-CĤPëPSPsC,PµPeP°PSCí.

P’PµPíP°C†PëP·CíPjP°P± **БĤ**“ CĤPµP·CíP»CHC,P°C,Pë CíPíPµC†PëC„C-C±PSPsPíPs
PrPsCíP»C-PrP¶PµPSPSCİ PíP·P°C”PjPsPrC-C— PjC-P¶ P»C-PeP°CĤCíCHPePëPjPë
P·P°CíPsP±P°PjPë PSPµ PíCĤPsPrPµPjPsPSCíC,CĤCíPíP°P»Pë P·PSP°C±PSPsPíPs
PíPíP»PëPíCí P±PµPíP°C†PëP·CíPjP°P±Cí PSP° C„P°CĤPjP°PePsPeC-PSPµC,PëPeCí
C-CĤPëPSPsC,PµPeP°PSCí C,P° PNëPsPíPs P°PeC,PëPíPSPsPíPs PjPµC,P°P±PsP»C-C,Cí
SN-38. PhPrPSP°Pe C†Pµ PSPµ PíPëPeP»CHC±P°C” P±CíPrCHC-ÇİPePsPíPs
PíC-PrPíPëC%PµPSPSCİ C,PsPeCíPëC±PSPsCíC,C- PíPSP°CíP»C-PrPsPe
C—C...PSC-C... C„P°CĤPjP°PePsP»PsPíC-C±PSPëC... PíP»P°CíC,PëPíPsCíC,PµPNë.

PíPµC,CíPeCíPëPjP°P± **БĤ**“ C-PSC„PsCĤPjP°C†C-Çİ C%PsPrPs PíPíP»PëPíCí
C†PµC,CíPeCíPëPjP°P±Cí PSP° PíCĤPsC„C-P»CH P±PµP·PíPµC±PSPsCíC,C-
C-CĤPëPSPsC,PµPeP°PSCí P°P±Ps PíCĤPs P°PSP°P»PsPíC-C±PSPëPNë PíPíP»PëPí
C-CĤPëPSPsC,PµPeP°PSCí PSP° C†PµC,CíPeCíPëPjP°P± PíC-PrCíCíC,PSCİ.

PhPSC,PëPSPµPsPíP»P°CíC,PëC±PSC- P·P°CíPsP±Pë (PíPeP»CHC±P°CHC±Pë
C„P»CíC†PëC,PsP·PëPS ÇİPe PíCĤPsP»C-PePë 5-C„C,PsCĤCíCĤP°C†PëP»Cí) **БĤ**“
PíPsP±C-C±PSC- PµC„PµPeC,Pë C-CĤPëPSPsC,PµPeP°PSCí, C,P°PeC- ÇİPe
PjC-C”P»PsCíCíPíCĤPµCíC-Çİ, PjPsP¶CíC,CH PíPsCíPëP»CHPíP°C,PëCíCİ C-PSC€PëPjPë
PíCĤPsC,PëPíCíC...P»PëPSPSPëPjPë PíCĤPµPíP°CĤP°C,P°PjPë, C%Ps PjP°CHC,CH
PíPsPrC-P±PSPëPNë PíCĤPsC„C-P»CH PíPsP±C-C±PSPëC... PµC„PµPeC,C-PI.

PhCíPsP±P»PëPíPsCíC,C- P·P°CíC,PsCíC±PíP°PSPSCİ.

P—P°CíC,PsCíPsPíCíPíP°C,Pë PíCĤPµPíP°CĤP°C, P†CĤPëPSPsC,PµPeP°PS PhPjP°PeCíP°
CíP»C-Pr PíPëPeP»CHC±PSPs Çí PíC-PrPrC-P»PµPSPSC-, C%Ps
CíPíPµC†C-P°P»C-P·CíC”C,CHCíCİ PSP° PíCĤPsPíPµPrPµPSPSC-
C†PëC,PsC,PsPeCíPëC±PSPsC— C...C-PjC-PsC,PµCĤP°PíC-C—. PµCĤPµPíP°CĤP°C, CíP»C-Pr
P·P°CíC,PsCíPsPíCíPíP°C,Pë PíPëPeP»CHC±PSPs PíC-Pr PePsPSC,CĤPsP»PµPj
PePíP°P»C-C„C-PePsPíP°PSPsPíPs P»C-PeP°CĤCİ, ÇİPePëPNë
CíPíPµC†C-P°P»C-P·CíC”C,CHCíCİ PSP° PíCĤPsPíPµPrPµPSPSC- PíCĤPsC,PëCĤP°PePsPíPsPíPs
C...C-PjC-PsC,PµCĤP°PíPµPíC,PëC±PSPsPíPs P»C-PeCíPíP°PSPSCİ.

P’CĤP°C...PsPíCíCHC±Pë C...P°CĤP°PeC,PµCĤ C,P° C±P°CíC,PsC,Cí CĤPsP·PíPëC,PeCí
PíPsP±C-C±PSPëC... CĤPµP°PeC†C-PNë, Çí PSPëP¶C±PµP·P°P·PSP°C±PµPSPëC...
PíPëPíP°PrPeP°C... P†CĤPëPSPsC,PµPeP°PS PhPjP°PeCíP° PSPµPsP±C...C-PrPSPs
P·P°CíC,PsCíPsPíCíPíP°C,Pë P»PëC€Pµ PíC-CíP»Çİ PsC†C-PSPePë
CíPíC-PíPíC-PrPSPsC€PµPSPSCİ PsC†C-PeCíPíP°PSPsC— PePsCĤPëCíC,C- C,P°

PjPsP¶P»PëPIPëC... C¶PëP·PëPeC-PI PIC-Pr P»C-PeCfPIP°PSPSC¶:

- PrP»C¶ P»C-PeCfPIP°PSPSC¶ PïP°C†C-C"PSC,C-PI C-P· C„P°PeC,PsC¶P°PjPë C¶PëP·PëPeCf, P·PsPeC¶PµPjP° PïP°C†C-C"PSC,C-PI C-P· PïPsPeP°P·PSPëPePsPj P·P°PiP°P»CHßPSPsPiPs C¶C,P°PSCf P·P° C-PSPrPµPeC¶PsPj P'PhPhP—, C%Ps PrPsC¶C-PIPSC¶C" 2;

- C¶ PsPeC¶PµPjPëC... C¶C-PrPeC-C¶PSPëC... PIPëPïP°PrPeP°C..., PePsP»Pë PIPIP°P¶P°C,CßC¶C¶, C%Ps PïP°C†C-C"PSC,Pë PSP°PIC¶C¶Pr C±Pë P±CfPrCfC,CH PrPsC,C¶PëPjCfPIP°C,PëC¶Cß C¶PµPePsPjPµPSPrP°C†C-PNë C%PsPrPs P»C-PeCfPIP°PSPSC¶ PïPsP±C-C±PSPëC... C¶PµP°PeC†C-PNë (PSPµPsP±C...C-PrPSC-C¶C,CHß PSPµPiP°PNëPSPsPiPs C,P° PrPsPIPiPsC,C¶PëPIP°P»PsPiPs P»C-PeCfPIP°PSPSC¶ PrC-P°C¶PµC— C¶ PïPsC"PrPSP°PSPSC- P· PIP¶PëPIP°PSPSC¶Pj PIPµP»PëPePsC— PeC-P»CHßPePsC¶C,C- C¶C-PrPëPSPë PSP° PïPsC±P°C,PeCf PIC-PrC¶C,C¶PsC±PµPSPsC— PrC-P°C¶PµC—); C,P°PePëPj PïP°C†C-C"PSC,P°Pj C¶PµPePsPjPµPSPrCfC"C,CHßC¶C¶ C¶PµC,PµP»CHßPSPµ C¶PïPsC¶C,PµC¶PµP¶PµPSPSC¶ PI C¶PjPsPIP°C... C¶C,P°C†C-PsPSP°C¶Cf.

PµC¶Pë P·P°C¶C,PsC¶CfPIP°PSPSC- C-C¶PëPSPsC,PµPeP°PSCf C¶Pe PjPsPSPsC,PµC¶P°PiC-C— PNëPsPiPs P·P°P·PIPëC±P°PNë PïC¶PëP·PSP°C±P°CßC,CHß P·P° PiC¶P°C„C-PePsPj PrPsP·CfPIP°PSCß PePsP¶PSC- 3 C,PëP¶PSC-. PhPrPSP°Pe C¶C...PµPjCf PrPsP·CfPIP°PSPSC¶ 1 C¶P°P· PSP° C,PëP¶PrPµPSCß PjPsP¶PSP° PIPëPePsC¶PëC¶C,PsPICfPIP°C,Pë PïP°C†C-C"PSC,P°Pj, C¶PePëPj PjPsP¶Pµ P·PSP°PrPsP±PëC,PëC¶C¶ P±C-P»CHßC¶ C¶PµC,PµP»CHßPSPµ C¶PïPsC¶C,PµC¶PµP¶PµPSPSC¶ P°P±Ps C¶PePëPj P·P°PiC¶PsP¶CfC" PsC¶PsP±P»PëPIP° PSPµP±PµP·PïPµPeP° PSPµPNëC,C¶PsPiPµPSC-C—.

P'C-PrC¶C,C¶PsC±PµPSP° PrC-P°C¶PµC¶.

PµP°C†C-C"PSC,C-PI C¶P»C-Pr PïPsPIC-PrPsPjPëC,Pë PïC¶Ps C¶PëP·PëPe C¶PsP·PIPëC,PeCf PIC-PrC¶C,C¶PsC±PµPSPsC— PrC-P°C¶PµC—, C%Ps PIPëPSPëPeP°C" P±C-P»CHßC¶ PSC-P¶ C±PµC¶PµP· 24 PiPsPrPëPSPë PiC-C¶P»C¶ P·P°C¶C,PsC¶CfPIP°PSPSC¶ PïC¶PµPïP°C¶P°C,Cf P†C¶PëPSPsC,PµPeP°PS PhPjP°PeC¶P° C,P° Cf P±CfPrCß-C¶PePëPNë C±P°C¶ PïPµC¶PµPr PSP°C¶C,CfPïPSPëPj PeCfC¶C¶PsPj P»C-PeCfPIP°PSPSC¶. PµC¶Pë PjPsPSPsC,PµC¶P°PiC-C— PjPµPrC-P°PSP° C¶PsP·PIPëC,PeCf PïPµC¶C¶PsPiPs PµPiC-P·PsPrCf C¶C-PrPePëC... PIPëPïPsC¶PsP¶PSPµPSCß C¶C,P°PSPsPIPëP»P° 5 PrPSC-PI P· PjPsPjPµPSC,Cf PIPIPµPrPµPSPSC¶ PïC¶PµPïP°C¶P°C,Cf P†C¶PëPSPsC,PµPeP°PS PhPjP°PeC¶P°. PµP°C†C-C"PSC,Pë PïPsPIPëPSPSC- PSPµ P·PIPsP»C-PeP°CßC±Pë PïPsPIC-PrPsPjPëC,Pë P»C-PeP°C¶Cß PïC¶Ps C¶PsP·PIPëC,PsPe PrC-P°C¶PµC— C,P° PSPµPiP°PNëPSPs C¶PsP·PïPsC±P°C,Pë PIC-PrPïPsPIC-PrPSCf C,PµC¶P°PiC-Cß.

P"Ps PiC¶CfPïPë PiC-PrPIPëC%PµPSPsPiPs C¶PëP·PëPeCf C¶PsP·PIPëC,PeCf PrC-P°C¶PµC— PSP°P»PµP¶P°C,CHß PïP°C†C-C"PSC,Pë, C¶PeC- C¶P°PSC-C¶Pµ PsC,C¶PëPjCfPIP°P»Pë PïC¶PsPjPµPSPµPICf C,PµC¶P°PiC-Cß P·PsPSPë P¶PëPIPsC,P° P°P±Ps C,P°P·P°, PïP°C†C-C"PSC,Pë, Cf C¶PePëC... PSP° PIPëC...C-PrPSPsPjCf C¶C-PIPSC- PSP°C¶IPSPëPNë PiC-PïPµC¶P»PµPNëPePsC†PëC,PsP·, PïP°C†C-C"PSC,Pë P·

C-PSPPrPμPeCfPsPj CfC,P°PSCr P·PrPsCfPsPIb[™] Cμ P·P° C€PeP°P»PsCf P'PhPhP— ≥ 2
C,P° P¶C-PSPePë. P—P° PIC-PrCfCrC,PSpScfC,C- PSp°P»PμP¶PSPsPiPs P»C-PeCfPIP°PSPSCμ
PrC-P°CfPμCμ PjPsP¶Pμ CfC,P°PSPsPiPëC,Pë P·P°PiCfPsP·Cr PrP»Cμ P¶PëC,C,Cμ,
PsCfPsP±P»PëPIPs CμPeC%Ps PIPsPSP° CfCrPiCfPsPIPsPrP¶CfC"C,ChCfCμ
PSPμPNëC,CfPsPiPμPSC-C"Cf.

PμC-CfP»Cμ PiPμCfC€PsPiPs PμPiC-P·PsPrCr CfC-PrPePëC...
PIPëPiPsCfPsP¶PSPμPSCf PiP°C†C-C"PSC,Cr CfP»C-Pr PSPμPiP°PNëPSPs
CfPsP·PiPsC†PëPSP°C,Pë PiCfPëPNëPsPj PIPμP»PëPePsC— PeC-P»ChPePsCfC,C-
CfC-PrPëPSPë, C%Ps PjC-CfC,PëC,Ch PμP»PμPeC,CfPsP»C-C,Pë, C,P°
PiCfPsPIPsPrPëC,Pë PIC-PrPiPsPIC-PrPSPμ PiCfPsC,PëPrC-P°CfPμPNëPSPμ
P»C-PeCfPIP°PSPSCμ. PμCfPsPIPsPrPëC,Pë PiCfPsC,PëPrC-P°CfPμPNëPSPμ
P»C-PeCfPIP°PSPSCμ PSPμPsP±C...C-PrPSPs Cr PIC-PrPrC-P»PμPSPSC-, PrPμ
PiP°C†C-C"PSC,Cr PIPsPrPëP»Pë P†CfPëPSPsC,PμPeP°PS PhPjP°PeCfP°. PμC-CfP»Cμ
PIPëPiPëCfPePë P· P»C-PeP°CfPSC- PiP°C†C-C"PSC,Cr CfP»C-Pr PsC,CfPëPjP°C,Pë
PiCfPëP·PSP°C†PμPSC- PiCfPμPiP°CfP°C,Pë, C%PsP± PjP°C,Pë PjPsP¶P»PëPIC-CfC,Ch
PiPsC†P°C,Pë P»C-PeCfPIP°PSPSCμ PrC-P°CfPμC— PsPrCfP°P·Cr PiC-CfP»Cμ C—C—
PIPëPSPëPePSPμPSPSCμ. PμCfC-Pj C,PsPiPs, PiP°C†C-C"PSC, PiPsPiPëPSPμPS
PiPsPIC-PrPsPjPëC,Pë PiCfPs PIPëPSPëPePSPμPSPSCμ PrC-P°CfPμC— CfPIPsC"PjCr
P»C-PeP°CfCf P°P±Ps P»C-PeP°CfCf PIC-PrPrC-P»PμPSPSCμ, PI CμPePsPjCr
PiP°C†C-C"PSC,Cr PIPsPrPëP»Pë P†CfPëPSPsC,PμPeP°PS PhPjP°PeCfP°.

P PμPePsPjPμPSPPrPsPIP°PSPμ PSP° CfChPsPiPsPrPSC- PiCfPsC,PëPrC-P°CfPμPNëPSPμ
P»C-PeCfPIP°PSPSCμ PiPsP»CμPiP°C" Cr P·P°CfC,PsCfCrPIP°PSPSC- PIPμP»PëPePëC...
PrPsP· P»PsPiPμCfP°PjC-PrCr (4 PjPi PSP° PiPμCfC€Pμ P·P°CfC,PsCfCrPIP°PSPSCμ,
PiPsC,C-Pj PiPs 2 PjPi C†PμCfPμP· PePsP¶PSC- 2 PiPsPrPëPSPë). P»C-PeCfPIP°PSPSCμ
CfP»C-Pr PiCfPsPIPsPrPëC,Pë PiCfPsC,CμPiPsPj 12 PiPsPrPëPS PiC-CfP»Cμ
PsCfC,P°PSPSCHPsPiPs PμPiC-P·PsPrCr CfC-PrPePëC... PIPëPiPsCfPsP¶PSPμPSCf.
PŸC...PμPjP° P»C-PeCfPIP°PSPSCμ PSPμ PiC-PrP»CμPiP°C" PjPsPrPëC,,C-PeP°C†C-CμPj.
P»PsPiPμCfP°PjC-Pr Cr C,P°PePëC... PrPsP·P°C... PSC- PI CμPePsPjCr CfP°P·C- PSPμ
CfP»C-Pr P·P°CfC,PsCfPsPICrPIP°C,Pë PrPsPIC€Pμ PSC-P¶ 48 PiPsPrPëPS Cr
P·PIb[™] CμP·PeCf P· CfPëP·PëPePsPj CfPsP·PIPëC,PeCf PiP°CfP°P»C-C,PëC†PSPsC—
PePëC€PePsPIPsC— PSPμPiCfPsC...C-PrPSPsCfC,C-; PIPsPrPSPsC†P°Cf
P»C-PeCfPIP°PSPSCμ PSPμ PiPsPiPëPSPSPs C,CfPëPiP°C,Pë PjPμPSC€Pμ PSC-P¶ 12
PiPsPrPëPS.

Pj CfP°P·C-, PePsP»Pë PrC-P°CfPμCμ CfCrPiCfPsPIPsPrP¶CfC"C,ChCfCμ
C,CμP¶PePsCf PSPμPNëC,CfPsPiPμPSC-C"Cf (PeC-P»ChPeC-CfC,Ch
PSPμPNëC,CfPsC,,C-P»C-PI PSPëP¶C†Pμ B B B B B B B B B B 500
PeP»C-C,PëPS/PjPj³), PrPsPrP°C,PePsPIPs PrPs PiCfPsC,PëPrC-P°CfPμPNëPSPsPiPs
P»C-PeCfPIP°PSPSCμ CfP»C-Pr P· PiCfPsC,,C-P»P°PeC,PëC†PSPsCf PjPμC,PsCf
P·P°CfC,PsCfPsPICrPIP°C,Pë P°PSC,PëP±C-PsC,PëPePë C€PëCfPsPePsPiPs
CfPiPμPeC,CfP° PrC-C—.

P"PsPrP°C,PePsPIPs PrPs P·P°CfC,PsCfCrPIP°PSPSCμ P°PSC,PëP±C-PsC,PëPeC-PI
PrP»Cμ P»C-PeCfPIP°PSPSCμ PrC-P°CfPμC— CfPμPePsPjPμPSPPrPsPIP°PSPs
PiPsCfPiC-C,P°P»C-P·CfPIP°C,Pë PiP°C†C-C"PSC,C-PI Cr C,P°PePëC...
PIPëPiP°PrPeP°C...:

РѹСѢСсС,СІІРІсРј Р»С-РєСрРІР°РSPSCІІ РїСѢРѹРїР°СѢР°С,РсРј Р†СѢРѢSPsС,РѹРєР°РSP
РђРјР°Р°Р°СІР° СѢРѹРєРсРјРѹРSPРРсРІР°РSPs С%РсС,РѢР¶РSPCІІ РєРсРSPC,СѢРсР»СѢРІР°С,РѢ
РїРсРєР°Р°РSPѢРєРѢ РєР»С-РSC-С†РSPsРїРс Р°РSP°Р»С-Р°Ср РєСѢРсРІС-. РѹР°С†С-С"РSC,С-РІ
СІР»С-С-Рр РїРсРїРѹСѢРѹРРР¶Р°С,РѢ РїСѢРс СѢРѢР°РѢРє СѢРсР°РІѢС,РєСр
РSPРѹР№С,СѢРсРїРѹРSPC-С— С,Р° РїСѢРс Р°РSP°С†СрС%С-СІС,Сђ РїР°СѢСІС†РєРѢ.
РќРѹРсР±С...С-РрSPs РSPРїР°РР№РSPs СѢРсР°РїРсС†РѢРSP°С,РѢ Р»С-РєСрРІР°РSPSCІІ
С,,РѹР±СѢРѢР»СђРSPsС— РSPРѹР№С,СѢРсРїРѹРSPC-С— (С,РѹРјРјРїРѹСѢР°С,СрСѢР° >38 В°С С,Р°
РєС-Р»СђРєС-СІС,Сђ РSPРѹР№С,СѢРсС,,С-Р»С-РІ ≤1000 РєР»С-С,РѢРс/РјРј³) РІ СрРјРсРІР°С...
СІС,Р°С†С-РсРSP°СѢСр Р° РІРSCрС,СѢС-СєРSCђРсРІРѹРSPSPѢРј РІРІРѹРРѹРSPSCІІРј
Р°РSPC,РѢР±С-РсС,РѢРєС-РІ СєРѢСѢРсРєРсРїРс СІРїРѹРєС,СѢР° РрС-С—. РѹР°С†С-С"РSC,Р°Рј
Р° СрСІРѢР»Р°Р°РРSPРѹРSPSCІІРјРѢ С,СІІР¶РєРсРїРс СІС,СрРїРѹРSPCІІ Р° Р±РсРєСр
СІРѢСІС,РѹРјРѢ РєСѢРсРІС- СѢРѹРєРсРјРѹРSPРРсРІР°РSPs Р°РSPѢР°РѢС,РѢ РрРсР°Ср РІ
РїРсРрР°Р»СђСєРѢС... С†РѢРєР»Р°Р°С... Р»С-РєСрРІР°РSPSCІІ (РрРѢРІ. СѢРсР°РрС-Р»
В«РЎРїРсСІС-Р± Р°Р°СІС,РсСІСрРІР°РSPSCІІ С,Р° РрРсР°РѢВ»). Рј РїР°С†С-С"РSC,С-РІ
Р° РрС-Р°СѢРѹС"Сђ С,СІІР¶РєРсРїРс СІС,СрРїРѹРSPCІІ РїС-РрРІѢС%СрС"С,СђСІСІ

$\text{P}_{\mu}\text{P}^{\circ}\text{C}^{\dagger}\text{C}-\text{C}^{\prime\prime}\text{PSC}, \text{P}^{\circ}\text{P}_{\text{j}} \text{C}-\text{P} \cdot \text{C}\overline{\text{H}}\text{C}-\text{PIPSP}_{\mu}\text{P}_{\text{j}} \text{P}^{\pm}\text{C}-\text{P} \gg \text{C}-\text{C}\overline{\text{H}}\text{C}^{\dagger}\text{P}^{\pm}\text{C}-\text{PSC}^{\dagger} \text{PIP}\ddot{\text{C}}\%_{\text{P}}\mu$
 $\text{PIP}_{\mu}\text{C}\overline{\text{H}}\text{C} \dots \text{PSC}\overline{\text{H}}\text{PsC}-\text{P}_{\text{j}}\text{P}_{\mu}\text{P}^{\dagger}\text{C}-\text{PSPsC}\overline{\text{H}}\text{P}_{\text{j}}\text{P}\ddot{\text{C}} \text{C}^{\dagger} 1,5\overline{\text{B}}^{\dagger}3 \text{C}\overline{\text{H}}\text{P}^{\circ}\text{P} \cdot \text{P}\ddot{\text{C}} \text{C}^{\dagger}\text{P} \gg \text{C}-\text{Pr}$
 $\text{C}\%_{\text{P}}\text{PsC}, \text{P}\ddot{\text{C}}\text{P}^{\dagger}\text{PSC}\overline{\text{H}} \text{PePsPSC}, \text{C}\overline{\text{H}}\text{PsP} \gg \text{C}\overline{\text{H}}\text{PIP}^{\circ}\text{C}, \text{P}\ddot{\text{C}} \text{P}\ddot{\text{C}}\text{PsPeP}^{\circ}\text{P} \cdot \text{PSP}\ddot{\text{C}}\text{PeP}\ddot{\text{C}} \text{PeP} \gg \text{C}-\text{PSC}-\text{C}^{\dagger}\text{PSPsPiPs}$
 $\text{P}^{\circ}\text{PSP}^{\circ}\text{P} \gg \text{C}-\text{P} \cdot \text{C}^{\dagger} \text{PeC}\overline{\text{H}}\text{PsPIC}-\text{C}^{\dagger} \text{P} \cdot \text{P}\overline{\text{I}}\overline{\text{B}}^{\dagger} \text{C}\overline{\text{H}}\text{P} \cdot \text{PeC}^{\dagger} \text{P} \cdot \text{C}-\text{P} \cdot \text{PSP}\ddot{\text{C}}\text{P}^{\dagger}\text{P}_{\mu}\text{PSPSC}\overline{\text{H}}\text{P}_{\text{j}}$
 $\text{PeP} \gg \text{C}-\text{C}\overline{\text{H}}\text{P}_{\mu}\text{PSC}^{\dagger}\text{C}^{\dagger} \text{C}-\text{C}\overline{\text{H}}\text{P}\ddot{\text{C}}\text{PSPsC}, \text{P}_{\mu}\text{PeP}^{\circ}\text{PSC}^{\dagger} (\text{PrP}\ddot{\text{C}}\text{PI}, \text{C}\overline{\text{H}}\text{PsP} \cdot \text{PrC}-\text{P} \gg$
 $\text{B} \ll \text{P}^{\circ}\text{C}\overline{\text{H}}\text{P}_{\text{j}}\text{P}^{\circ}\text{PePsPeC}-\text{PSP}_{\mu}\text{C}, \text{P}\ddot{\text{C}}\text{PeP}^{\circ}\text{B} \gg), \text{C}\%_{\text{P}}\text{Ps} \text{P}\ddot{\text{C}}-\text{PrPIP}\ddot{\text{C}}\%_{\text{C}}\text{C}^{\dagger}\text{C}^{\prime\prime} \text{C}\overline{\text{H}}\text{P}\ddot{\text{C}}\text{P} \cdot \text{P}\ddot{\text{C}}\text{Pe}$

PiPμPjP°C,PsC,PsPeCΓPëC±PSPsCΓC,C-. PκPμ CΓP»C-Pr PIPiPsPrPëC,Pë P†CḡPëPSPsC,PμPeP°PS PḡPjP°PeCΓP° PİP°C†C-C”PSC,P°Pj C-P· CḡC-PIPSμPj P±C-P»C-CḡC†P±C-PSC† PIPëC%Pμ PIPμCḡC...PSCḡPsC— PjPμP¶C- PSPsCḡPjPë P±C-P»CHC€ PSC-P¶ C† 3 CḡP°P·Pë (PrPëPI. CḡPsP·PrC-P» B«PμCḡPsC,PëPİPsPeP°P·P°PSPSCİB»).

PκCζPrPsC,P° C,P° P±P»CḡPIP°PSPSCİ.

PμPμCḡPμPr PePsP¶PSPëPj PIPiPμPrPμPSPSCİPj P»C-PeP°CḡCΓCHḡPePsPiPs P·P°CΓPsP±C† P†CḡPëPSPsC,PμPeP°PS PḡPjP°PeCΓP° CḡPμPePsPjPμPSP†C†C”C,CHCΓCİ P· PİCḡPsC,,C-P»P°PeC,PëC±PSPsCḡ PjPμC,PsCḡ P·P°CΓC,PsCΓPsPIC†PIP°C,Pë PİCḡPsC,PëP±P»CḡPIP°P»CHḡPSC- PİCḡPμPİP°CḡP°C,Pë. PμCḡPë P·P°CΓC,PsCΓC†PIP°PSPSC- PİCḡPμPİP°CḡP°C,C† C†P°CΓC,Ps PİPsPIC-PrPsPjP»CİP»PsCΓCİ PİCḡPs PIPëPSPëPePSPμPSPSCİ PSC†PrPsC,Pë C,P° P±P»CḡPIP°PSPSCİ. PμP°C†C-C”PSC,Pë P· P±P»CḡPIP°PSPSCİPj, C%Ps CΓC†PİCḡPsPiPsPrP¶C†C”C,CHCΓCİ PIC-PrCΓC,CḡPsC±PμPSPsCḡ PrC-P°CḡPμC”Cḡ, PİPsC,CḡPμP±C†CḡC,CH PiPsCΓPİC-C,P°P»C-P·P°C†C-C— C† PSP°PNḡPePsCḡPsC,C€PëPNḡ C,PμCḡPjC-PS PrP»Cİ PİCḡPsPiPμPrPμPSPSCİ PSP°P»PμP¶PSPsPiPs P»C-PeC†PIP°PSPSCİ.

P”PsCΓC,CḡPëPNḡ C...PsP»C-PSPμCḡPiC-C±PSPëPNḡ CΓPëPSP†CḡPsPj.

P—P° PIC-PrCΓC†C,PSPsCΓC,C- PeP»C-PSC-C±PSPëC... PİCḡPsC,PëPİPsPeP°P·P°PSCḡ (PrPëPI. CḡPsP·PrC-P» B«PμPsP±C-C±PSC- CḡPμP°PeC†C-C—B») C† CḡP°P·C- CḡPsP·PIPëC,PeC† PiPsCΓC,CḡPsPiPs C...PsP»C-PSPμCḡPiC-C±PSPsPiPs CΓPëPSP†CḡPsPjC† (CḡP°PSPSCİ PrC-P°CḡPμCİ C† PePsPjP±C-PSP°C†C-C— P· CḡC-P·PSPsPjP°PSC-C,PSPëPjPë C-PSC€PëPjPë PsP·PSP°PeP°PjPë C,P° CΓPëPjPİC,PsPjP°PjPë, C,P°PePëPjPë CİPe PİC-PrPIPëC%PμPSP° PİC-C,P»PëPIC-CΓC,CH, CΓPİP°P·PjPë C† P¶PëPIPsC,C-, PjC-PsP· C,P° PİC-PrPIPëC%PμPSPμ CΓP»PëPSPsPiPëPrC-P»PμPSPSCİ) CΓP»C-Pr PIPiPsPrPëC,Pë 0,25 PjPi P°C,CḡPsPİC-PSC† CΓC†P»CHC,,P°C,C† PİC-PrC€PeC-CḡPSPs. PμPsCİPIC† C†PëC... CΓPëPjPİC,PsPjC-PI, CİPeC- PjPsP¶C†C,CH CΓPİPsCΓC,PμCḡC-PİP°C,PëCΓCİ PİCḡPsC,CİPiPsPj P°P±Ps PsPrCḡP°P·C† PİC-CΓP»Cİ C-PSC,,C†P·C-C— C-CḡPëPSPsC,PμPeP°PSC†, PİPsPIḡḡ™ CİP·C†CḡC,CH P· P°PSC,PëC...PsP»C-PSPμCΓC,PμCḡP°P·PSPsCḡ P°PeC,PëPIPSC-CΓC,Cḡ PİPsC±P°C,PePsPiPsC— CΓPİPsP»C†PePë C-CḡPëPSPsC,PμPeP°PSC†. PμPμCḡPμPrP±P°C†P°C”C,CHCΓCİ, C%Ps PİCḡPë P·P°CΓC,PsCΓC†PIP°PSPSC- P±C-P»CHC€ PIPëCΓPsPePëC... PrPsP· C-CḡPëPSPsC,PμPeP°PSC† C†P°CΓC,PsC,P° C—C... PIPëPSPëPePSPμPSPSCİ P·CḡPsCΓC,P°C,PëPjPμ.

P>C-PeC†PIP°C,Pë PİP°C†C-C”PSC,C-PI P· P°CΓC,PjPsCḡ CΓP»C-Pr P· PsP±PμCḡPμP¶PSC-CΓC,Cḡ. PμP°C†C-C”PSC,P°Pj C-P· PiPsCΓC,CḡPëPj C...PsP»C-PSPμCḡPiC-C±PSPëPj CΓPëPSP†CḡPsPjPsPj C,CİP¶PePsPiPs CΓC,C†PİPμPSCİ PİPμCḡPμPr PePsP¶PSPëPj PSP°CΓC,C†PİPSPëPj P·P°CΓC,PsCΓC†PIP°PSPSCİPj PİCḡPμPİP°CḡP°C,C† P†CḡPëPSPsC,PμPeP°PS PḡPjP°PeCΓP° CḡPμPePsPjPμPSP†PsPIP°PSPs PİCḡPsPiPsPrPëC,Pë PİCḡPsC,,C-P»P°PeC,PëC±PSPμ P»C-PeC†PIP°PSPSCİ P°C,CḡPsPİC-PSC† CΓC†P»CHC,,P°C,PsPj.

P PsP·P»P°PrPë P· P±PsPeCζ PrPëC...P°P»CHḡPSPsC— CΓPëCΓC,PμPjPë.

PμC-Pr C†P°CΓ P»C-PeC†PIP°PSPSCİ PrP°PSPëPj PİCḡPμPİP°CḡP°C,PsPj PjPsP¶P»PëPIC- PSPμC±P°CΓC,C- PIPëPİP°PrPePë CḡPsP·PIPëC,PeC† C-PSC,PμCḡCΓC,PëC†C-P°P»CHḡPSPsC— C...PIPsCḡPsP±Pë P»PμPiPμPSC-PI, C%Ps PİCḡPsCİPIP»CİC”C,CHCΓCİ C† PIPëPİP»CİPrC- C†C,PIPsCḡPμPSPSCİ C-PSC,,C-P»CHḡC,CḡP°C,C-PI C† P»PμPiPμPSCİC..., P°P»Pμ P·P°C...PIPsCḡCḡPIP°PSPSCİ PjPsP¶Pμ PİCḡPëP·PIPsPrPëC,Pë PrPs P»PμC,P°P»CHḡPSPsPiPs PSP°CΓP»C-PrPeC†. P”Ps C,,P°PeC,PsCḡC-PI CḡPëP·PëPeC†, PjPsP¶P»PëPIPs PİPsPIḡḡ™ CİP·P°PSPëC... C-P· CḡPsP·PIPëC,PePsPj C-PSC,PμCḡCΓC,PëC†C-P°P»CHḡPSPsC—

C...PIPsCḡPsP±Pë P»PµPiPµPSC-PI, PIC-PrPSPsCíCḡC,CH P·P°CíC,PsCíCíPIP°PSPSCḡ
PíCḡPµPíP°CḡP°C,C-PI, C,PsPeCíPëC±PSPëC... C%PsPrPs P»PµPiPµPSC-PI, PíCḡPsPjPµPSPµPICí
C,PµCḡP°PíC-Cḡ C,P° PePsP»PsPSC-C"íC,PëPjCíP»CḡCḡC±C- C,,P°PeC,PsCḡPë. P—P°
PíP°CíC-C"PS C,P°PjPë P·PSP°CḡPIPSPëPjPë C,,P°PeC,PsCḡP°PjPë CḡPëP·PëPeCí PrPs
PíPsC±P°C,PeCí C,P° PíC-Pr C±P°Cí P»C-PeCíPIP°PSPSCḡ CíP»C-Pr CḡPµC,PµP»CHPSPs
CíPíPsCíC,PµCḡC-PíP°C,Pë C%PsPrPs PIPëPSPëPePSPµPSPSCḡ CíPëPjPíC,PsPjC-PI P·
P±PsPeCí PrPëC...P°P»CHPSPsC— CíPëCíC,PµPjPë.

P·PeCíC,CḡP°PIP°P·P°CíC-Cḡ.

PíPsC±P° C-CḡPëPSPsC,PµPeP°PS PSPµ PSP°P»PµPḡPëC,CH PrPs
PíCḡPµPíP°CḡP°C,C-PI, C%Ps PíCḡPëP·PIPsPrCḡC,CH PrPs CíC,PIPsCḡPµPSPSCḡ
PSPµPeCḡPsP·Cí C,PeP°PSPëPS, PíCḡPµPíP°CḡP°C, CíP»C-Pr PIPsPrPëC,Pë P·
PsP±PµCḡPµPḡPSC-CíC,Cḡ C,P° PePsPSC,CḡPsP»CḡPIP°C,Pë CíC,P°PS PjC-CíCíCḡ
C-PSC,,CíP·C-C— C%PsPrPs PsP·PSP°Pe P·P°PíP°P»PµPSPSCḡ. Pj PIPëPíP°PrPeCí
PíPsC,CḡP°PíP»CḡPSPSCḡ PíCḡPµPíP°CḡP°C,Cí P·P° PjPµPḡC- CíCíPrPëPSPë
CḡPµPePsPjPµPSPPrPsPIP°PSPs PíCḡPsPjPëC,Pë PjC-CíCíPµ C-PSC,,CíP·C-C— C,P°
PíCḡPëPeP»P°CíC,Pë P»C-Pr.

PµP°CíC-C"PS C,Pë P»C-C,PSCHPsPiPs PIC-PeCé.

Pj P·PIBḡ™ CḡP·PeCí P· P±C-P»CHCéPsCḡ C±P°CíC,PsC,PsCḡ P·PSPëPḡPµPSPSCḡ
P±C-PsP»PsPíC-C±PSPëC... C,,CíPSPeCíC-PNḡ, P·PsPeCḡPµPjP° C,,CíPSPeCíC-C—
PíPµC±C-PSPePë, PíP°CíC-C"PS C,P°Pj P»C-C,PSCHPsPiPs PIC-PeCí PrPsP·Cí
PíCḡPµPíP°CḡP°C,Cí PíCḡPëPSPsC,PµPeP°PS PḡPjP°PeCíP° CíP»C-Pr PíC-PrP±PëCḡP°C,Pë P·
PsP±PµCḡPµPḡPSC-CíC,Cḡ (PrPëPI. CḡPsP·PrC-P» B«PḡPíPsCíC-P±
P·P°CíC,PsCíCíPIP°PSPSCḡ C,P° PrPsP·PëB»).

PíCḡPsPSC-C±PSC- P·P°PíP°P»CHPSC- P·P°C...PIPsCḡCḡPIP°PSPSCḡ PePëCéPµC±PSPëPeCé
C,P°/P°P±Ps PsP±CíC,CḡCéPeCíC-Cḡ PePëCéPµC±PSPëPeCé.

PµP°CíC-C"PS C,P°Pj PSPµ CíP»C-Pr P·P°CíC,PsCíCíPIP°C,Pë PíCḡPëPSPsC,PµPeP°PS
PḡPjP°PeCíP° PrPsPePë PSP°CḡPIPSP° PsP±CíC,CḡCíPeCíC-Cḡ PePëCéPµC±PSPëPeCí (PrPëPI.
CḡPsP·PrC-P» B«PµCḡPsC,PëPíPsPeP°P·P°PSPSCḡB»).

PµP°CíC-C"PS C,Pë P· PíPsCḡCéCéPµPSPSCḡPjPë C,,CéPSPeCíC-C— PSPëCḡPsPe.

PḡPíPsCíC,PµCḡC-PíP°P»PsCíCḡ PíC-PrPIPëC%PµPSPSCḡ CḡC-PIPSḡ
CíPëCḡPsPIP°C,PePsPIPsPiPs PeCḡPµP°C,PëPSC-PSCí P°P±Ps P°P·PsC,Cí CíPµC±PsPIPëPSPë
PeCḡPsPIC-. P' CíP»Pë PIPëPíP°PrPePë PíPsCíC,CḡPsC— PSPëCḡPePsPIPsC—
PSPµPrPsCíC,P°C,PSPsCíC,C-. PíC- CḡPIPëC%P° P·P°P·PIPëC±P°PNḡ P±CíP»Pë
PíPsPIBḡ™ CḡP·P°PSC- P· CíCíPeP»P°PrPSPµPSPSCḡPjPë C-PSC,,PµPeCíC-PNḡ P°P±Ps
P·PSPµPIPsPrPSPµPSPSCḡPj PsCḡPíP°PSC-P·PjCí PIPSP°CíP»C-PrPsPe PSCíPrPsC,Pë,
P±P»CḡPIP°PSPSCḡ C±Pë PrC-P°CḡPµC—. PḡCḡC-Pj C,PsPiPs, PSP°PrC...PsPrPëP»Pë
PíPsPIC-PrPsPjP»PµPSPSCḡ PíCḡPs PíPsPsPrPëPSPsPeC- PIPëPíP°PrPePë PíPsCḡCíCéPµPSPSCḡ
C,,CíPSPeCíC-C— PSPëCḡPsPe PIPSP°CíP»C-PrPsPe CíPëPSPPrCḡPsPjCí P»C-P·PëCíCí
PíCíC...P»PëPSPë.

P PsP·P»P°PrPë P· P±PsPeCé CíPµCḡCíCḡ.

PµC-CíP»Cḡ P·P°CíC,PsCíCíPIP°PSPSCḡ C-CḡPëPSPsC,PµPeP°PSCí
CíPíPsCíC,PµCḡC-PíP°P»PëCíCḡ PIPëPíP°PrPePë CḡPsP·PIPëC,PeCí C-CéPµPjC-C—

PjC-PsPeP°CḡPrP°, PiPμCḡPμPIP°P¶PSPs Cr PiP°C†C-C''PSC,C-PI C-P· PSP°C¶PIPSpPpPpPē
P·P°C...PIPsCḡCḡPIP°PSPSC¶PjPē CḡPμCḡC†C¶, C-PSC€PēPjPē PIC-PrPsPjPēPjPē
C,,P°PeC,PsCḡP°PjPē CḡPēP·PēPeCr CḡPsP·PIPēC,PeCr P·P°C...PIPsCḡCḡPIP°PSCḡ
CḡPμCḡC†C¶ C,P° Cr PiP°C†C-C''PSC,C-PI, C¶PeC- CḡP°PSC-C€Pμ PsC,CḡPēPjC†PIP°P»Pē
C†PēC,PsC,PsPeCḡPēC†PSC† C...C-PjC-PsC,PμCḡP°PiC-Cḡ (PrPēPI. CḡPsP·PrC-P»
B«PμPsP±C-C†PSC- CḡPμP°PeC†C-C-B»). P'C-PrPiPsPIC-PrPSPs, PiP°C†C-C''PSC,Pē P·
PIC-PrPsPjPēPjPē C,,P°PeC,PsCḡP°PjPē CḡPēP·PēPeCr PiPsC,CḡPμP±CrCḡC,CH
CḡPμC,PμP»CHPSPsPiPs PSP°PiP»C¶PIPrCr. PŸP»C-Pr PIP¶PēC,Pē P·P°C...PsPrC-PI PrP»C¶
P·PIPμPrPμPSPSC¶ PrPs PjC-PSC-PjC†PjC† PIC†C-C... C,,P°PeC,PsCḡC-PI CḡPēP·PēPeCr, C%Ps
PiC-PrPrP°CḡC,CHCḡC¶ CḡPμPiC†P»CḡPIP°PSPSCḡ (PSP°PiCḡPēPeP»P°Pr, PiP°P»C-PSPSC¶,
P°CḡC,PμCḡC-P°P»CHPSP° PiC-PiPμCḡC,PμPSP·C-C¶ C,P° PiC-PiPμCḡP»C-PiC-PrPμPjC-C¶).

P PsP·P»P°PrPē P· P±PsPeCž CḡCžPrPēPS.

PJ PiP°C†C-C''PSC,C-PI, C¶PeC- PjP°P»Pē PjPSPsP¶PēPSPSC- C,,P°PeC,PsCḡPē CḡPēP·PēPeCr
PSP° PrPsPrP°C,PsPe PrPs PsCḡPSPsPIPSPsPiPs PSPsPIPSC†C,PIPsCḡPμPSPSC¶,
P·P°CḡC,PsCḡC†PIP°PSPSC¶ C-CḡPēPSPsC,PμPeP°PSC† PI CḡC-PrPeC-CḡPSPēC...
PIPēPiP°PrPeP°C... PiPsPiBḡ™ C¶P·C†PIP°P»Pē P· PIPēPSPēPePSPμPSPSC¶Pj
C,CḡPsPjP±PsPμPjP±PsP»C-C†PSPēC... CrCḡPeP»P°PrPSPμPSCḡ (P»PμPiPμPSPμPIP°
PμPjP±PsP»C-C¶, PIPμPSPsP·PSPēPμ C,CḡPsPjP±PsP· C,P° P°CḡC,PμCḡC-P°P»CHPSP°
C,CḡPsPjP±PsPμPjP±PsP»C-C¶).

PμCḡPsPjPμPSPμPIP° C,PμCḡP°PiC-C¶.

PμP°C†C-C''PSC,Pē, C¶PeC- CḡP°PSC-C€Pμ PsC,CḡPēPjC†PIP°P»Pē PsPiCḡPsPjC-PSPμPSPSC¶
PsCḡPIP°PSC-PI PjP°P»PsPiPs C,P°P·P° P°P±Ps C†PμCḡPμPIPSPsC— PiPsCḡPsP¶PSPēPSPē,
PIC...PsPrC¶C,CH PrPs PiCḡC†PiPē PiC-PrPIPēC%PμPSPsPiPs CḡPēP·PēPeCr CḡPsP·PIPēC,PeCr
PjC-C''P»PsCḡC†PiCḡPμCḡC-C— PSP° C,P»C- P»C-PeC†PIP°PSPSC¶ C-CḡPēPSPsC,PμPeP°PSPsPj.
P>C-PeP°CḡC- PjP°CḡC,CH P· PsP±PμCḡPμP¶PSC-CḡC,Cḡ P·P°CḡC,PsCḡPsPIC†PIP°C,Pē
PrP°PSPēPμ P»C-PeP°CḡCḡCHPePēPμ P·P°CḡC-P± PiP°C†C-C''PSC,P°Pj, C¶PeC- PI
PjPēPSC†P»PsPjC† PsC,CḡPēPjC†PIP°P»Pē PμPeCḡC,PμPSCḡPēPIPSC† PiCḡPsPjPμPSPμPIC†
C,PμCḡP°PiC-Cḡ (PSP°PiCḡPēPeP»P°Pr, PsPiCḡPsPjC-PSPμPSPSC¶ > 25 %
PeC-CḡC,PePsPIPsPiPs PjPsP·PeCr PiCḡPsC,C¶PiPsPj 6 C,PēP¶PSC-PI PrPs PiPsC†P°C,PeCr
P»C-PeC†PIP°PSPSC¶ C-CḡPēPSPsC,PμPeP°PSPsPj). P|C-Pμ PiCḡC†PiC- PiP°C†C-C''PSC,C-PI
PjPsP¶Pμ P·PSP°PrPsP±PēC,PēCḡC¶ PePsCḡPēPiC†PIP°PSPSC¶ PrPsP·Pē PiCḡPμPiP°CḡP°C,C†
(PrPēPI. CḡPsP·PrC-P» B«PŸPiPsCḡC-P± P·P°CḡC,PsCḡC†PIP°PSPSC¶ C,P° PrPsP·PēB»).

PμPμCḡC-PsPr PiPsPrCžPIP°PSPSC¶ PiCḡCžPrPrCḡ.

PJ P·PiBḡ™ C¶P·PeCr P· PjPsP¶P»PēPIC-CḡC,Cḡ PIPēPSPēPePSPμPSPSC¶ PiPsP±C-C†PSPēC...
CḡPμP°PeC†C-Pμ Cr PiCḡC†PrPSPēC... PrC-C,PμPμ PiPsPrC†PIP°PSPSC¶ PiCḡC†PrPrCḡ
CḡP»C-Pr PiCḡPēPiPēPSPēC,Pē PSP° C†P°Cḡ P»C-PeC†PIP°PSPSC¶ PiCḡPμPiP°CḡP°C,PsPj
(PrPēPI. CḡPsP·PrC-P»Pē B«PμCḡPsC,PēPiPsPeP°P·P°PSPSC¶B» C,P°
B«P—P°CḡC,PsCḡC†PIP°PSPSC¶ Cr PiPμCḡC-PsPr PIP°PiC-C,PSPsCḡC,C- P°P±Ps
PiPsPrC†PIP°PSPSC¶ PiCḡC†PrPrCḡB»).

PJ P·PiBḡ™ C¶P·PeCr P· PjPsP¶P»PēPIC-CḡC,Cḡ PiPμPSPsC,PsPeCḡPēC†PSPsCḡC,C-
P¶C-PSPeP°Pj CḡPμPiCḡPsPrC†PeC,PēPIPSPsPiPs PIC-PeCr CḡPμPePsPjPμPSPPrPsPIP°PSPs
PIPēPePsCḡPēCḡC,PsPIC†PIP°C,Pē PIPēCḡPsPePsPμC,,PμPeC,PēPIPSC- P·P°CḡPsP±Pē
PePsPSC,CḡP°C†PμPiC†C-C— PiC-Pr C†P°Cḡ P»C-PeC†PIP°PSPSC¶ C,P° PiCḡPsC,C¶PiPsPj 6
PjC-CḡC¶C†C-PI PiC-CḡP»C¶ P·P°CḡC,PsCḡC†PIP°PSPSC¶ PsCḡC,P°PSPSCHPsC— PrPsP·Pē
C-CḡPēPSPsC,PμPeP°PSC†.

PJ P·PIB[™] CΠP·PeC_r P· PjPsPΠP»PëPIC-C_rC, C_h PiPμPSPsC, PsPeC_rPëC±PSPsC_rC, C- C_rP»C-Pr C_hPμPePsPjPμPSPPrC_rPIP° C, Pë PiP°C_rC-C" PSC, P°Pj-C±PsP»PsPIC-PeP°Pj C-P· PiP°C_hC, PSPμC_hPeP°PjPë-PΠC-PSPeP°PjPë P· C_hPμPiC_hPsPrC_rPeC, PëPIPSPëPj PiPsC, PμPSC_rC-P°P»PsPj PIPëPePsC_hPëC_rC, PsPIC_rPIP° C, Pë PμC,, PμPeC, PëPIPSC- P·P°C_rPsP±Pë PePsPSC, C_hP°C_rPμPiC_rC-C— PiC-Pr C±P°C_r P»C-PeC_rPIP°PSPSCΠ C, P° PiC_hPsC, CΠPiPsPj 3 PjC-C_rCΠC_rC-PI PiC-C_rP»CΠ P·P°C_rC, PsC_rC_rPIP°PSPSCΠ PsC_rC, P°PSPSCHbPsC— PrPsP·Pë C-C_hPëPSPsC, PμPeP°PSC_r (PrPëPI. C_hPsP·PrC-P» B«P-P°C_rC, PsC_rC_rPIP°PSPSCΠ C_r PiPμC_hC-PsPr PIP°PiC-C, PSPsC_rC, C- P°P±Ps PiPsPrC_rPIP°PSPSCΠ PiC_hC_rPrPrC_hB»).

P†PSC€C- C,, P°PeC, PsC_hPë.

P_hC_rPeC-P»C_hPePë PiC_hPμPiP°C_hP° C, PjC-C_rC, PëC, C_h D-C_rPsC_hP±C-C,, CΠPePëPN₂ C" PrPΠPμC_hPμP»PsPj C,, C_hC_rPeC, PsP·Pë, PN₂PsPiPs PSPμ PjPsPΠPSP° P·P°C_rC, PsC_rPsPIC_rPIP° C, Pë PrP»CΠ P»C-PeC_rPIP°PSPSCΠ PiP°C_rC-C" PSC, C-PI P·C- C_rPiP°PrPePsPIPsC_h PSPμPiPμC_hPμPSPsC_rPëPjC-C_rC, C_h C,, C_hC_rPeC, PsP·Pë (PŸP_kP_α). PJ PSPμPjPsPIP»CΠC, C, P° PjP°P»PμPSC_hPePëC... PrC-C, PμPN₂ PIC-PePsPj PrPs 2 C_hPsPeC-PI PjPsPΠPμ C%Pμ PSPμ P±C_rC, Pë PrC-P°PiPSPsC_rC, PsPIP°PSPs PŸP_kP_α. P>C-PeP°C_hC_rCHbPeC- P·P°C_rPsP±Pë, CΠPeC- PjC-C_rC, CΠC, C_h C,, C_hC_rPeC, PsP·C_r C, P° PIPIPsPrCΠC, C_hC_rCΠ PIPSC_rC, C_hC-C€PSC_hPsPIPμPSPSPs, PjPsPΠC_rC, C_h PjP° C, Pë PSPμP±PμP·PiPμC±PSC- PrP»CΠ PΠPëC, C, CΠ PμC,, PμPeC, Pë C_r P»C_hPrPμPN₂ P·C- PŸP_kP_α, C, PsPjC_r C—C... PSPμ C_rP»C-Pr PIPIPsPrPëC, Pë C, P°PePëPj PiP°C_rC-C" PSC, P°Pj, CΠPeC%Ps PSPμPjP°C" PiPsC_rC, C_hPsC— PeP»C-PSC-C±PSPsC— PSPμPsP±C...C-PrPSPsC_rC, C- P°P±Ps PSPμPjP°C" P°P»C_hC, PμC_hPSP° C, PëPIPë.

PμPμC_hPμPr P·P°C_rC, PsC_rC_rPIP°PSPSCΠPj C_rCHbPsPiPs P»C-PeP°C_hC_rCHbPePsPiPs P·P°C_rPsP±C_r C_r PePsPΠPSPsPiPs PiP°C_rC-C" PSC, P° C_rP»C-Pr P·C-P±C_hP° C, Pë P°PSP°PjPSPμP· C%PsPrPs C_rPëPjPiC, PsPjC-PI PŸP_kP_α.

P_hPrPSPsC±P°C_rPSPμ PIPIPμPrPμPSPSCΠ C-C_hPëPSPsC, PμPeP°PSC_r P· C_rPëP»C_hPSPëPj C-PSPiC-P±C-C, PsC_hPsPj (PSP°PiC_hPëPeP»P°Pr, PePμC, PsPePsPSP°P·PsP»PsPj) P°P±Ps C-PSPPrC_rPeC, PsC_hPsPj (PSP°PiC_hPëPeP»P°Pr, C_hPëC,, P°PjPiC-C_rPëPSPsPj, PeP°C_hP±P°PjP°P·PμPiC-PSPsPj, C,, PμPSPsP±P°C_hP±C-C, P°P»PsPj, C,, PμPSC-C, PsC—PSPsPj, P°PiP°P»C_rC, PsPjC-PrPsPj) CYP3A4 PjPsPΠPμ P·PjC-PSPëC, Pë PjPμC, P°P±PsP»C-P·Pj C-C_hPëPSPsC, PμPeP°PSC_r C- PN₂PsPiPs C_rP»C-Pr C_rPSPëPeP° C, Pë (PrPëPI. C_hPsP·PrC-P» B«P·P·P°C" PjPsPrC-CΠ P· C-PSC€PëPjPë P»C-PeP°C_hC_rCHbPePëPjPë P·P°C_rPsP±P°PjPë C, P° C-PSC€C- PIPëPrPë PIP·P°C" PjPsPrC-PN₂B»).

P_αP»P°PePsPSPë P†C_hPëPSPsC, PμPeP°PS P_hPjP°PeC_rP° PsP±B[™]C" PjPsPj PSP°PiPsPIPSPμPSPSCΠ 2 PjP» C, P° 5 PjP» PjC-C_rC, CΠC, C_h PjPμPSC€Pμ 1 PjPjPsP»C_h (23 PjPi)/PrPsP·C_r PSP° C, C_hC-C_h, C, PsP±C, Ps PiC_hP°PeC, PëC±PSPs PIC-P»C_hPSC- PIC-Pr PSP° C, C_hC-C_h.

P_αP»P°PePsPS P†C_hPëPSPsC, PμPeP°PS P_hPjP°PeC_rP° PsP±B[™]C" PjPsPj PSP°PiPsPIPSPμPSPSCΠ 15 PjP» PjC-C_rC, PëC, C_h 36 PjPi/PrPsP·C_r PSP° C, C_hC-C_h. PŸP»C-Pr P±C_rC, Pë PsP±PμC_hPμPΠPSPëPj PiC_hPë P·P°C_rC, PsC_rC_rPIP°PSPSC- PiP°C_rC-C" PSC, P°Pj, CΠPeC- P·P°C_rC, PsC_rPsPIC_rC_hC, C_h PSP° C, C_hC-PN₂- PePsPSC, C_hPsP»C_hPsPIP°PSC_r PrC-C" C, C_r.

*P—P°CÍC,PsCÍCžPIP°PSPSCÍ Cž PiPµCĤC-PsPr PIP°PiC-C,PSPsCÍC,C- P°P±Ps
PiPsPrCžPIP°PSPSCÍ PiCĤCžPrPrCĤ.*

PµPsPSC,CĤP°C†PµPiC†C-CÍ.

PJ P·PIBĤ™ CÍP·PeCÍ P· PjPsP¶P»PëPIC-CÍC,CĤ PiPµPSPsC,PsPeCÍPëC‡PSPsCÍC,C-
P¶C-PSPeP°Pj CĤPµPiCĤPsPrCÍPeC,PëPIPSsPiPs PIC-PeCÍ
CĤPµPePsPjPµPSPPrPsPIP°PSPs PIPëPePsCĤPëCÍC,PsPICÍPIP°C,Pë
PIPëCÍPsPePsPµC,,PµPeC,PëPIPSC- P·P°CÍPsP±Pë PePsPSC,CĤP°C†PµPiC†C-C— PiC-Pr
C‡P°CÍ P»C-PeCÍPIP°PSPSCÍ C,P° PiCĤPsC,CÍPiPsPj 6 PjC-CÍCÍC†C-PI PiC-CÍP»CÍ
P·P°CÍC,PsCÍCÍPIP°PSPSCÍ PsCÍC,P°PSPSCHPsC— PrPsP·Pë
C-CĤPëPSPsC,PµPeP°PSCÍ (PrPëPI. CĤPsP·PrC-P» B«PhCÍPsP±P»PëPIPsCÍC,C-
P·P°CÍC,PsCÍCÍPIP°PSPSCÍB»).

PJ P·PIBĤ™ CÍP·PeCÍ P· PjPsP¶P»PëPIC-CÍC,CĤ PiPµPSPsC,PsPeCÍPëC‡PSPsCÍC,C-
CÍP»C-Pr CĤPµPePsPjPµPSPPrCÍPIP°C,Pë PiP°C†C-C”PSC,P°Pj-C‡PsP»PsPIC-PeP°Pj C-P·
PiP°CĤC,PSPµCĤPeP°PjPë-P¶C-PSPeP°PjPë P· CĤPµPiCĤPsPrCÍPeC,PëPIPSPëPj
PiPsC,PµPSC†C-P°P»PsPj PIPëPePsCĤPëCÍC,PsPICÍPIP°C,Pë PµC,,PµPeC,PëPIPSC-
P·P°CÍPsP±Pë PePsPSC,CĤP°C†PµPiC†C-C— PiC-Pr C‡P°CÍ P»C-PeCÍPIP°PSPSCÍ C,P°
PiCĤPsC,CÍPiPsPj 3 PjC-CÍCÍC†C-PI PiC-CÍP»CÍ P·P°CÍC,PsCÍCÍPIP°PSPSCÍ
PsCÍC,P°PSPSCHPsC— PrPsP·Pë C-CĤPëPSPsC,PµPeP°PSCÍ (PrPëPI. CĤPsP·PrC-P»
B«PhCÍPsP±P»PëPIPsCÍC,C- P·P°CÍC,PsCÍCÍPIP°PSPSCÍB»).

PµPµCĤC-PsPr PIP°PiC-C,PSPsCÍC,C-.

P”P°PSC- C%PsPrPs P·P°CÍC,PsCÍCÍPIP°PSPSCÍ C-CĤPëPSPsC,PµPeP°PSCÍ
PIP°PiC-C,PSPëPj P¶C-PSPeP°Pj PsP±PjPµP¶PµPSC-. PJ PrPsCÍP»C-PrP¶PµPSPSCÍC...
PSP° C,PIP°CĤPëPSP°C... P±CÍP»Ps PiCĤPsPrPµPjPsPSCÍC,CĤPsPIP°PSPs, C%Ps
C-CĤPëPSPsC,PµPeP°PS C‡PëPSPëC,CĤ PµPjP±CĤC-PsC,PsPeCÍPëC‡PSCÍ C,P°
C,PµCĤP°C,PsPiPµPSPSCÍ PrC-CĤ. P’PµCĤCÍC‡Pë PrPs CÍPIP°PiPë
CĤPµP·CÍP»CĤC,P°C,Pë PrPsCÍP»C-PrP¶PµPSCĤ PSP° C,PIP°CĤPëPSP°C... C,P°
PjPµC...P°PSC-P·Pj PrC-C— C-CĤPëPSPsC,PµPeP°PSCÍ, PSPµ CÍP»C-Pr
P·P°CÍC,PsCÍPsPICÍPIP°C,Pë PrP°PSPëPµ PiCĤPµPiP°CĤP°C, PiC-Pr C‡P°CÍ
PIP°PiC-C,PSPsCÍC,C-, PsCÍPsP±P»PëPIPs CÍ PiPµCĤC€PsPjCÍ C,CĤPëPjPµCÍC,CĤC-,
P·P° PIPëPSCÍC,PePsPj PSP°PiP°P»CĤHPSPsC— PiPsC,CĤPµP±Pë. P-C-PSPeP°Pj
PrC-C,PsCĤPsPrPSPsPiPs PIC-PeCÍ PSPµ P·P°CÍC,PsCÍPsPICÍPIP°C,Pë
C-CĤPëPSPsC,PµPeP°PS, PrPsPePë PSPµ P±CÍPrPµ PIPëPeP»CĤC‡PµPSP°
PIP°PiC-C,PSC-CÍC,CĤ. PkPµPsP±C...C-PrPSPs CÍPSPëPeP°C,Pë PIP°PiC-C,PSPsCÍC,C-,
CÍPeC%Ps C...C,PsCÍCĤ C-P· PiP°CĤC,PSPµCĤC-PI PsC,CĤPëPjCÍC”
C-CĤPëPSPsC,PµPeP°PS.

P’PiP»PëPI PSP° CĤPµPiCĤPsPrCžPeC,PëPIPSCž C,,CžPSPeC†C-CĤ.

P†PSC,,PsCĤPjP°C†C-CÍ C%PsPrPs PIPiP»PëPICÍ C-CĤPëPSPsC,PµPeP°PSCÍ PSP°
CĤPµPiCĤPsPrCÍPeC,PëPIPSCÍ C,,CÍPSPeC†C-CĤ P»CĤPrPëPSPë PIC-PrCÍCÍC,PSCÍ. PJ
PrPsCÍP»C-PrP¶PµPSPSCÍC... PSP° C,PIP°CĤPëPSP°C... P±CÍP»Pë
PrPsPeCÍPjPµPSC,P°P»CĤHPSPs P·P°CĤPµC”CÍC,CĤPsPIP°PSC- PiPsP±C-C‡PSC-

$P^{\circ}P \pm Ps$ $PiC - C \uparrow P \gg C \downarrow$ $C \uparrow P s P \cdot C \uparrow P \ddot{e} P S P_{\mu} P S P S C \downarrow C$ " $Pi P s P j C - C, P S P \ddot{e} P N_{\circ}$
 $Pi C \uparrow P_{\mu} C \uparrow P \ddot{e} P i C - C, P^{\circ} C,,$ $Pi C \uparrow P_{\mu} P i P^{\circ} C \uparrow P^{\circ} C,$ $C \uparrow P \gg C - P r$ $C r C, P \ddot{e} P \gg C - P \cdot C r P i P^{\circ} C, P \ddot{e} P \cdot$
 $P r P s C, C \uparrow P \ddot{e} P j P^{\circ} P S P S C \downarrow P j$ $C \uparrow C, P^{\circ} P S P r P^{\circ} C \uparrow C, P S P \ddot{e} C \dots$ $Pi C \uparrow P s C \uparrow P_{\mu} P r C r C \uparrow$
 $C r C, P \ddot{e} P \gg C - P \cdot P^{\circ} C \uparrow C - C -$ $C \uparrow P \ddot{e} C, P s C, P s P e C \uparrow P \ddot{e} C \uparrow P S P \ddot{e} C \dots$ $Pi C \uparrow P_{\mu} P i P^{\circ} C \uparrow P^{\circ} C, C - P i.$

$P'' P s C, C \uparrow P \ddot{e} P j C r C \uparrow C \uparrow P \ddot{e} C \uparrow C \uparrow P S P s C \uparrow P j$ $P^{\circ} C \uparrow P_{\mu} P i C, P \ddot{e} P e P \ddot{e},$ $P i C - P r P \pm P \ddot{e} C \uparrow P^{\circ} C \uparrow C, C \uparrow$
 $P e P^{\circ} P \gg C - P \pm C \uparrow P s P i P^{\circ} P S P \ddot{e} P j$ $C \in P i C \uparrow P \ddot{e} C \uparrow P s P j$ $P S P_{\mu} P s P \pm C \dots C - P r P S C r$
 $P e C - P \gg C \uparrow P e C - C \uparrow C, C \uparrow C \uparrow P s P \cdot C \uparrow P \ddot{e} P S C r$ $Pi C \uparrow P_{\mu} P i P^{\circ} C \uparrow P^{\circ} C, C r$ $P \uparrow C \uparrow P \ddot{e} P S P s C, P_{\mu} P e P^{\circ} P S$
 $P \uparrow P j P^{\circ} P e C \uparrow P^{\circ} P \cdot C,, P \gg P^{\circ} P e P s P S P^{\circ} C, P^{\circ}$ $P i P i P s P r C \downarrow C, C \uparrow P r P s P \cdot C r$ $P i$ $P i P^{\circ} P e P_{\mu} C, P^{\circ} P \pm P s$
 $P i P \gg C \downarrow C \in P e C r$ $P s P \pm B \uparrow^{\text{TM}} C'' P j P s P j$ $250 P j P \gg,$ $C \% P s$ $P j C - C \uparrow C, P \ddot{e} C, C \uparrow C$ $0,9 \%$ $C \uparrow P s P \cdot C \uparrow P \ddot{e} P S$
 $P S P^{\circ} C, C \uparrow C - C \uparrow C$ $C \dots P \gg P s C \uparrow P \ddot{e} P r C r$ $P^{\circ} P \pm P s$ 5% $C \uparrow P s P \cdot C \uparrow P \ddot{e} P S$ $P i P \gg C \uparrow P e P s P \cdot P \ddot{e}.$
 P $P_{\mu} C, P_{\mu} P \gg C \uparrow P S P s$ $P i P_{\mu} C \uparrow P_{\mu} P j C - C \in C r C \uparrow C, C \uparrow C$ $C \uparrow P s P \cdot C \uparrow P \ddot{e} P S,$ $P i C \uparrow C r C \uparrow P S C r$
 $P s P \pm P_{\mu} C \uparrow C, P^{\circ} C \uparrow C \uparrow P \ddot{e} C'' P j P S C - C \uparrow C, C \uparrow C.$

P $P_{\mu} P e P s P j P_{\mu} P S P r P s P i P^{\circ} P S C -$ $P r P s P \cdot P \ddot{e}.$

$P_{\mu} C \uparrow P \ddot{e}$ $P j P s P S P s C, P_{\mu} C \uparrow P^{\circ} P i C - C -$ $Pi C \uparrow P_{\mu} P i P^{\circ} C \uparrow P^{\circ} C, P \uparrow C \uparrow P \ddot{e} P S P s C, P_{\mu} P e P^{\circ} P S$
 $P \uparrow P j P^{\circ} P e C \uparrow P^{\circ} P \cdot P^{\circ} P \cdot P i P \ddot{e} C \uparrow P^{\circ} P N_{\circ}$ $Pi C \uparrow P \ddot{e} P \cdot P S P^{\circ} C \uparrow P^{\circ} C \uparrow C, C \uparrow C$ 1 $C \uparrow P^{\circ} P \cdot P S P^{\circ}$ 3
 $C, P \ddot{e} P \uparrow P S C -.$ $P' P s P r P S P s C \uparrow P^{\circ} C \uparrow$ $P i P^{\circ} C \uparrow C - C'' P S C, P^{\circ} P j,$ $C \downarrow P e P \ddot{e} P j$ $P j P s P \uparrow P_{\mu}$
 $P \cdot P S P^{\circ} P r P s P \pm P \ddot{e} C, P \ddot{e} C \uparrow C \downarrow$ $P \pm C - P \gg C \uparrow C \in$ $C \uparrow P_{\mu} C, P_{\mu} P \gg C \uparrow P S P \ddot{e} P N_{\circ}$ $P S P^{\circ} P i P \gg C \downarrow P r$ $P^{\circ} P \pm P s$
 $C \downarrow P e C -$ $P \cdot P S P^{\circ} C \dots P s P r C \downarrow C, C \uparrow C \uparrow C \downarrow$ $C r$ $P i C \uparrow C r P i C -$ $P i C - P r P i P \ddot{e} C \% P_{\mu} P S P s P i P s$
 $C \uparrow P \ddot{e} P \cdot P \ddot{e} P e C r$ $C \uparrow P s P \cdot P i P \ddot{e} C, P e C r$ $C, C \downarrow P \uparrow P e P s C -$ $P S P_{\mu} P N_{\circ} C, C \uparrow P s P i P_{\mu} P S C - C -,$
 $P j P s P \uparrow P S P^{\circ}$ $C \uparrow P s P \cdot P i P \gg C \downarrow P S C r C, P \ddot{e}$ $C \% P s C, P \ddot{e} P \uparrow P S P_{\mu} P i C r$ $C \uparrow C \dots P_{\mu} P j C r$
 $P \cdot P^{\circ} C \uparrow C, P s C \uparrow C r P i P^{\circ} P S P S C \downarrow$ $Pi C \uparrow P_{\mu} P i P^{\circ} C \uparrow P^{\circ} C, C r$ $(P r P \ddot{e} P i. C \uparrow P s P \cdot P r C - P \gg$
 $B \ll P \alpha P^{\circ} C \uparrow P j P^{\circ} P e P s P \gg P s P i C - C \uparrow P S C -$ $P i P \gg P^{\circ} C \uparrow C, P \ddot{e} P i P s C \uparrow C, C - B \gg).$

*$P_{\mu} P s P S P s C, P_{\mu} C \uparrow P^{\circ} P i C - C \downarrow$ $(P r P \gg C \downarrow P i P^{\circ} C \uparrow C - C'' P S C, C - P i, C \downarrow P e C -$ $C \uparrow P^{\circ} P S C - C \in P_{\mu}$
 $P s C, C \uparrow P \ddot{e} P j C \uparrow P i P^{\circ} P \gg P \ddot{e} P \gg C - P e C \uparrow P i P^{\circ} P S P S C \downarrow).$*

P $P_{\mu} P e P s P j P_{\mu} P S P r P s P i P^{\circ} P S P^{\circ}$ $P r P s P \cdot P^{\circ}$ $Pi C \uparrow P_{\mu} P i P^{\circ} C \uparrow P^{\circ} C, C r$ $P \uparrow C \uparrow P \ddot{e} P S P s C, P_{\mu} P e P^{\circ} P S$
 $P \uparrow P j P^{\circ} P e C \uparrow P^{\circ} C \uparrow C, P^{\circ} P S P s P i P \ddot{e} C, C \uparrow C$ $350 P j P i / P j^2$ $P i P s P i P_{\mu} C \uparrow C \dots P S C -$ $C, C - P \gg P^{\circ},$
 $P i P i P_{\mu} P r P_{\mu} P S P \ddot{e} C \dots$ $C \in P \gg C \downarrow C \dots P s P j$ $P i P S C r C, C \uparrow C - C \in P S C \uparrow P s P i P_{\mu} P S P S P s C -$ $C - P S C,, C r P \cdot C - C -$
 $C, C \uparrow P \ddot{e} P i P^{\circ} P \gg C - C \uparrow C, C \uparrow C$ $30 B \uparrow^{\text{TM}} 90 C \dots P i$ $C \uparrow P_{\mu} C \uparrow P_{\mu} P \cdot$ $P e P s P \uparrow P S C -$ $3 C, P \ddot{e} P \uparrow P S C -$ $(P r P \ddot{e} P i.$
 $C \uparrow P s P \cdot P r C - P \gg$ $B \ll P \alpha C \uparrow P s P \pm P \gg P \ddot{e} P i P s C \uparrow C, C -$ $P \cdot P^{\circ} C \uparrow C, P s C \uparrow C r P i P^{\circ} P S P S C \downarrow B \gg).$

*$P_{\mu} P s P j P \pm C - P S P s P i P^{\circ} P S P^{\circ}$ $C, P_{\mu} C \uparrow P^{\circ} P i C - C \downarrow$ $(P r P \gg C \downarrow P i P^{\circ} C \uparrow C - C'' P S C, C - P i, C \downarrow P e C -$
 $C \uparrow P^{\circ} P S C - C \in P_{\mu} P S P_{\mu} P s C, C \uparrow P \ddot{e} P j C \uparrow P i P^{\circ} P \gg P \ddot{e} P \gg C - P e C \uparrow P i P^{\circ} P S P S C \downarrow).$*

$P \cdot C,, P_{\mu} P e C, P \ddot{e} P i P S C - C \uparrow C, C \uparrow C$ C, P° $P \pm P_{\mu} P \cdot P i P_{\mu} P e C r$ $P \cdot P^{\circ} C \uparrow C, P s C \uparrow C r P i P^{\circ} P S P S C \downarrow$
 $C - C \uparrow P \ddot{e} P S P s C, P_{\mu} P e P^{\circ} P S C r$ $C r$ $P e P s P j P \pm C - P S P^{\circ} C \uparrow C - C -$ $P \cdot$ $5 - P \alpha P j$ C, P° $P \alpha P_{\mu}$
 $P s C \uparrow C - P S C \uparrow P i P^{\circ} P \gg P \ddot{e} P \cdot P^{\circ}$ $P S P \ddot{e} P \uparrow C \uparrow P_{\mu} P \cdot P^{\circ} P \cdot P S P^{\circ} C \uparrow P_{\mu} P S P s C \uparrow C$ $C \uparrow C \dots P_{\mu} P j P s C \uparrow$
 $P r P s P \cdot C r P i P^{\circ} P S P S C \downarrow$ $(P r P \ddot{e} P i. C \uparrow P s P \cdot P r C - P \gg$ $B \ll P \alpha P^{\circ} C \uparrow P j P^{\circ} P e P s P r P \ddot{e} P S P^{\circ} P j C - P e P^{\circ} B \gg).$
 P $P_{\mu} P e P s P j P_{\mu} P S P r P s P i P^{\circ} P S P^{\circ}$ $P r P s P \cdot P^{\circ}$ $C - C \uparrow P \ddot{e} P S P s C, P_{\mu} P e P^{\circ} P S C r$ $C \uparrow C, P^{\circ} P S P s P i P \ddot{e} C, C \uparrow C$
 $180 P j P i / P j^2$ 1 $C \uparrow P^{\circ} P \cdot P S P^{\circ}$ $2 C, P \ddot{e} P \uparrow P S C -$ $C r$ $P i P \ddot{e} P i P \gg C \downarrow P r C -$
 $P i P S C r C, C \uparrow C - C \in P S C \uparrow P s P i P_{\mu} P S P S P s C -$ $C - P S C,, C r P \cdot C - C -$ $P i C \uparrow P s C, C \downarrow P i P s P j$ $30 B \uparrow^{\text{TM}} 90$
 $C \dots P i P \ddot{e} P \gg P \ddot{e} P S, P i C - C \uparrow P \gg C \downarrow$ $C \uparrow P s P i P s$ $P i P i P s P r C \downarrow C, C \uparrow C$ $P \alpha P_{\mu}$ $C -$ $5 - P \alpha P j.$
 $P \uparrow P S C,, P s C \uparrow P j P^{\circ} C \uparrow C - C \uparrow C$ $Pi C \uparrow P s P r P s P \cdot P \ddot{e} C -$ $C \uparrow P i P s C \uparrow P s P \pm P \ddot{e}$ $C \uparrow C r P i C r C, P S C \uparrow P s P i P s$
 $P i P i P_{\mu} P r P_{\mu} P S P S C \downarrow$ $C \uparrow P_{\mu} C, C r P e C \uparrow P \ddot{e} P j P^{\circ} P \pm C r$ $P j P s P \uparrow P S P^{\circ}$ $P \cdot P S P^{\circ} P N_{\circ} C, P \ddot{e}$ $P i$
 $P e P s C \uparrow P s C, P e C - P N_{\circ}$ $C \dots P^{\circ} C \uparrow P^{\circ} P e C, P_{\mu} C \uparrow P \ddot{e} C \uparrow C, P \ddot{e} C \uparrow C -$ $P r P^{\circ} P S P s P i P s$

P»C-PeP°CḡCḡCHPePsPiPs P·P°CḡPsP±Cḡ. P—P°P·PIPëC±P°PNë
 P·P°CḡC,PsCḡPsPICḡCḡC,CH C,P°PeCḡ Pḡ PrPsP·Cḡ C-CḡPëPSPsC,PμPeP°PSCḡ, CḡPe C-
 PI PīPsPīPμCḡPμPrPSC-C... PeCḡCḡCḡP°C... P»C-PeCḡPIP°PSPSCḡ C-P·
 P·P°CḡC,PsCḡCḡPIP°PSPSCḡPj CḡC...PμPj, C%Ps PIPeP»CḡC±P°CḡC,CH
 C-CḡPëPSPsC,PμPeP°PS. P†CḡPëPSPsC,PμPeP°PS CḡP»C-Pr PIPsPrPëC,Pë PSPμ
 CḡP°PSC-CḡPμ PSC-Pḡ C±PμCḡPμP· 1 PiPsPrPëPSCḡ PīC-CḡP»Cḡ
 P·P°PeC-PSC±PμPSPSCḡ C-PSC,,CḡP·C-C— C†PμC,CḡPeCḡPëPjP°P±Cḡ. P”P»Cḡ
 PsC,CḡPëPjP°PSPSCḡ C-PSC,,PsCḡPjP°C†C-C— PīCḡPs PrPsP·CḡPIP°PSPSCḡ C,P°
 CḡPīPsCḡPsP±Pë P·P°CḡC,PsCḡCḡPIP°PSPSCḡ P±PμPIP°C†PëP·CḡPjP°P±Cḡ,
 P·PIPμCḡPSC-C,CHCḡCḡ PrPs PePsCḡPsC,PePsC— C...P°CḡP°PeC,PμCḡPëCḡC,PëPePë
 PrP°PSPsPiPs P»C-PeP°CḡCḡCHPePsPiPs P·P°CḡPsP±Cḡ. P†PSC,,PsCḡPjP°C†C-Cḡ
 PīCḡPs PrPsP·CḡPIP°PSPSCḡ C,P° P·P°CḡC,PsCḡCḡPIP°PSPSCḡ
 C-CḡPëPSPsC,PμPeP°PSCḡ PI PePsPjP±C-PSP°C†C-C— P· PeP°PīPμC†PëC,P°P±C-PSPsPj
 PrPëPI. Cḡ CḡPsP·PrC-P»C- B«P»P°CḡPjP°PePsP»PsPiC-C±PSC- PIP»P°CḡC,PëPIPsCḡC,C-B»
 C,P° Cḡ PIC-PrPīPsPIC-PrPSPëC... CḡPsP·PrC-P»P°C... PePsCḡPsC,PePsC—
 C...P°CḡP°PeC,PμCḡPëCḡC,PëPePë PeP°PīPμC†PëC,P°P±C-PSCḡ.

PḡPsCḡPμPeC†C-Cḡ PrPsP·Pë.

P†CḡPëPSPsC,PμPeP°PS PḡPjP°PeCḡP° CḡP»C-Pr PIPsPrPëC,Pë PīC-CḡP»Cḡ
 P°PrPμPePIP°C,PSPsPiPs P·PSPëPePSPμPSPSCḡ CḡCḡC-C... PīPsP±C-C±PSPëC...
 CḡPμP°PeC†C-PNë PrPs CḡC,CḡPīPμPSCḡ 0 P°P±Ps 1 P·P° CḡPeP°P»PsCḡ NCI-CTC
 (P·P°PīP°P»CHPSC- PeCḡPëC,PμCḡC-C— PsC†C-PSPePë C,PsPeCḡPëC±PSPsCḡC,C-
 PḡP°C†C-PsPSP°P»CHPSPsPiPs C-PSCḡC,PëC,CḡC,Cḡ CḡP°PeCḡ) C,P° PīC-CḡP»Cḡ
 PīPsPIPSPsPiPs PīCḡPëPīPëPSPμPSPSCḡ PīPsPīBḡ™ CḡP·P°PSPsC— P· P»C-PeCḡPIP°PSPSCḡPj
 PrC-P°CḡPμC—

PḡP° PīPsC±P°C,PeCḡ PSP°CḡC,CḡPīPSPsPiPs PeCḡCḡCḡCḡ PIPIPμPrPμPSPSCḡ
 CḡP»CḡC...PsPj C-PSC,,CḡP·C-C— PrPsP·Cḡ PīCḡPμPīP°CḡP°C,Cḡ
 P†CḡPëPSPsC,PμPeP°PS PḡPjP°PeCḡP° C,P° 5-PḡPJ, CḡPeC%Ps
 P·P°CḡC,PsCḡPsPICḡCḡC,CHCḡCḡ, CḡP»C-Pr P·PSPëPḡCḡPIP°C,Pë P·P°P»PμPḡPSPs PIC-Pr
 PīCḡPsCḡPIC-PI PīPsP±C-C±PSPëC... CḡPμP°PeC†C-PNë PSP°PNëC,CḡPḡC±PsPiPs
 CḡC,CḡPīPμPSCḡ, C%Ps CḡPīPsCḡC,PμCḡC-PiP°P»PëCḡCḡ PīC-Pr C±P°Cḡ
 PīPsPīPμCḡPμPrPSCḡPsC— C-PSC,,CḡP·C-C—. PḡP»C-Pr PIC-PrPeP»P°CḡC,Pë PīPsC±P°C,PsPe
 P»C-PeCḡPIP°PSPSCḡ PSP° 1Bḡ“2 C,PëPḡPSC- PrP»Cḡ P·PSPëPePSPμPSPSCḡ
 PīPsPīBḡ™ CḡP·P°PSPëC... P· P»C-PeCḡPIP°PSPSCḡPj PīPsP±C-C±PSPëC... CḡPμP°PeC†C-PNë.

PμCḡPë CḡPsP·PIPëC,PeCḡ PSPëPḡC±PμP·P°P·PSP°C±PμPSPëC... PīPsP±C-C±PSPëC...
 CḡPμP°PeC†C-PNë PrPsP·Cḡ PīCḡPμPīP°CḡP°C,Cḡ P†CḡPëPSPsC,PμPeP°PS PḡPjP°PeCḡP°
 C,P°/P°P±Ps 5-PḡPJ, CḡPeC%Ps P·P°CḡC,PsCḡPsPICḡCḡC,CHCḡCḡ, CḡP»C-Pr P·PSPëP·PëC,Pë
 PSP° 15Bḡ“20 %:

- PīPμPjP°C,PsC,PsPeCḡPëC±PSC-CḡC,CH (PSPμPNëC,CḡPsPīPμPSC-Cḡ IV
 CḡC,CḡPīPμPSCḡ, C,,PμP±CḡPëP»CHPSP° PSPμPNëC,CḡPsPīPμPSC-Cḡ
 (PSPμPNëC,CḡPsPīPμPSC-Cḡ IIIBḡ“IV CḡC,CḡPīPμPSCḡ, C%Ps
 CḡCḡPīCḡPsPIPPrPḡCḡCḡ,CHCḡCḡ PīP°CḡCḡC±PePsCḡ IIBḡ“IV CḡC,CḡPīPμPSCḡ),
 C,CḡPsPjP±PsC†PëC,PsPīPμPSC-Cḡ C,P° P»PμPNëPePsPīPμPSC-Cḡ (IV CḡC,CḡPīPμPSCḡ));

- PSPμPīPμPjP°C,PsP»PsPiC-C±PSP° C,PsPeCḡPëC±PSC-CḡC,CH (IIIBḡ“IV
 CḡC,CḡPīPμPSCḡ).

РҮР»С-Рr PrPsC,СҲРөРјСrPIP°С,РөСГГЦ ЦҲРµРePsPjPµPSPrP°С†С-РN₂ Р·
PjPsPrPөC,,С-РeP°С†С-С— PrPsP·Рө С†РµC,СrPeCГРөРјP°P±Сr PиCҲРө РN₂PsPiPs
Р·Р°СГГC,PsCГГCрPIP°PSPSC- Pи РePsPjP±С-РSP°С†С-С— Р· С-СҲРөPSPsC,РµРeP°PSPsPj
Р·РиC-РrPSPs Р· С-РSC,,PsCҲРјP°С†С-С"СҲ, РSP°PIPµPrPµPSPsCҲ Pи РePsCҲPsC,PeC-РN₂
С...P°СҲР°РeC,РµCҲРөCГГC,РөC†С- С†РµC,СrPeCГРөРјP°P±Сr.

Р†PSC,,PsCҲРјP°С†С-СҲ PиCҲPs PjPsPrPөC,,С-РeP°С†С-СҲ PrPsP·Рө P±РµPIP°С†РөР·СrPjP°P±Сr
PиCҲРө РePsPjP±С-РSPsPIP°PSPsPjCр P»С-РeCрPIP°PSPSC- P±РµPIP°С†РөР·СrPjP°P±PsPj Р·
С-СҲРөPSPsC,РµРeP°PSPsPj/5-РαPj/РαРҗ PjPsP¶PSP° Р·PSP°РN₂C,Рө Pи РePsCҲPsC,PeC-РN₂
С...P°СҲР°РeC,РµCҲРөCГГC,РөC†С- P±РµPIP°С†РөР·СrPjP°P±Сr.

РµP°С†С-С"PSC,Р°Pj PиC-РePsPj PиC-Рr 65 СҲPsPeC-Pи PиCҲРө Р·Р°СГГC,PsCГГCрPIP°PSPSC-
С-СҲРөPSPsC,РµРeP°PSCр C,Р° РeP°PиPµC†РөC,Р°P±С-РSCр СҲРµРePsPjPµPSPrCрC,СҲCГГЦ
Р·PSPөP¶CрPIP°С,Рө PrPsP·Cр РeP°PиPµC†РөC,Р°P±С-РSCр PrPs 800 PjPi/Pj² PиPsPIPµCҲC...PSC-
C,С-Р»P° 2 СҲР°Р·Рө РSP° PrPsP±Сr. Р"Р»CЦ С-РSC,,PsCҲРјP°С†С-С— PиCҲPs
РePsCҲРөPиCрPIP°PSPSCЦ PrPsP·Рө Cр СҲР°Р·Рө- РePsPjP±С-РSPsPIP°PSPsC— C,РµCҲР°РиC-С—
Р·PIPµCҲPSC-С,СҲCГГЦ PrPs РePsCҲPsC,РePsC— С...P°СҲР°РeC,РµCҲРөCГГC,РөPePө
РeP°PиPµC†РөC,Р°P±С-РSCр.

РҮCҲРөPIP°P»С-СГГC,СҲ Р»С-РeCрPIP°PSPSCЦ.

Р>С-РeCрPIP°PSPSCЦ PиCҲРµPиP°СҲР°Р·РөC,PsPj P†CҲРөPSPsC,РµРeP°PS РҗPjP°PeCГР° СГР»С-Рr
PиCҲPsPrPsPIP¶CрPIP°С,Рө PrPs PsP±BҲ™ C"PeC,РөPIPSPsPiPs PиCҲPsPиCҲРµCГГCрPIP°PSPSCЦ
Р·Р°С...PIPsCҲCҲPIP°PSPSCЦ Р°P±Ps PrPs СҲPsP·PIPөC,PeCр PsP·PSP°Pe
PSPµPиCҲРөPиCрCГГC,РөPjPsC— C,PsPeCГРөC±PSPsCГГC,С-.

РµP°С†С-С"PSC,Рө Р· PиPsCҲCзC€PµPSPSCЦPjPө C,,CзPSPeC†С-С— PиPµC±С-РSPePө.

РҲPsPSPsC,РµCҲР°РиC-СЦ.

- РµP°С†С-С"PSC,Р°Pj Р· С-РSPrPµPeCГРPsPj Р·Р°PиP°P»СҲPSPsPiPs CГГC,Р°PSCр ≤ 2 Р·Р°
C€PeP°P»PsCҲ Р'РҗPҗP— PиPsC±P°С,РePsPICр PrPsP·Cр P»С-РeP°CҲCГГCҲPePsPiPs
Р·Р°СГГPsP±Сr P†CҲРөPSPsC,РµРeP°PS РҗPjP°PeCГР° PSPµPsP±С...С-РrPSPs
PIPөР·PSP°С±P°С,Рө Р·Р° СҲC-PIPSµPj P±С-Р»С-СҲCрP±С-РSCр Pи РeCҲPsPIC- (PиCҲРө
Р·Р±С-С»СҲC€PµPSPSC- СҲC-PIPSЦ P±С-Р»С-СҲCрP±С-РSCр PIPөC%Pµ
PIPµCҲC...PSCҲPsC— PjPµP¶C- PSPsCҲРјPө PSPµ P±С-Р»СҲC€Pµ PSC-Р¶ Cр 3 СҲР°Р·РөPө). Pj
C,Р°PePөC... PиP°С†С-С"PSC,С-Pи Р· PиC-PиPµCҲР±С-Р»С-СҲCрP±С-РSPµPjC-С"СҲ C,Р°
PиCҲPsC,СҲPsPjP±С-РSPsPIPөPj C±P°CГГPsPj, P±С-Р»СҲC€PөPj PSP° 50 %,
PeP»С-СҲРµPSCГ C-СҲРөPSPsC,РµРeP°PSCр Р·PSPөP¶CрC",СҲCГГЦ (PрPөPи.
CҲPsP·PрC-Р» B«PαP°CҲРјP°PePsPeC-РSPµC,РөPeP°B»), PIPSP°CГР»С-РrPsPe C±PsPiPs
Р·CҲPsCГГC,Р°С" СҲРөP·PөPe CҲPsP·PIPөC,PeCр PиPµPjP°С,PsC,PsPeCГРөC±PSPsCГГC,С-.
РҮPsPjCр C,Р°PeC-РN₂ PeP°С,РµPiPsCҲC-С— PиP°С†С-С"PSC,С-Pи CГР»С-Рr
C%PsC,РөP¶PSCЦ РePsPSC,СҲPsP»CҲPIP°С,Рө PиPsPeP°P·PSPөPePө
PeP»С-РSC-С±PSPsPiPs Р°PSP°P»С-Р·Cр РeCҲPsPIC-.

- РµP°С†С-С"PSC,Р°Pj С-Р· СҲC-PIPSµPj P±С-Р»С-СҲCрP±С-РSCр PIPөC%Pµ
PIPµCҲC...PSCҲPsC— PjPµP¶C- PSPsCҲРјPө PSPµ P±С-Р»СҲC€ PSC-Р¶ Cр 1,5 СҲР°Р·РөPөPө
CҲРµРePsPjPµPSPrPsPIP°PSP° PrPsP·Р° PиCҲРµPиP°СҲР°Р·РөC,Ср CГГC,Р°PSPsPIPөC,СҲ 350 PjPi/Pj²
PиPsPIPµCҲC...PSC- C,С-Р»P°.

- P_μP°C†C-C''PSC,P°Pj C-P· C₇C-PIPS_μPj P±C-P»C-C₇C†P±C-PSC† PIPëC%P_μ
PIP_μC₇C...PSC_HPsC— PjP_μP¶C- PSp_sC₇PjPë C† 1,5B₇“3 C₇P°P·Pë C₇P_μPePsPjP_μPSPrPsPIP°PSP°
PrPsP·P° C†C,P°PSPsPIPëC,CH 200 PjPi/Pj² PīPsPIP_μC₇C...PSC- C,C-P»P°.

- P_μP°C†C-C''PSC,P°Pj C-P· C₇C-PIPS_μPj P±C-P»C-C₇C†P±C-PSC† PIPëC%P_μ
PIP_μC₇C...PSC_HPsC— PjP_μP¶C- PSp_sC₇PjPë P±C-P»CHC€ PSC-P¶ C† 3 C₇P°P·Pë PSp_μ
C†P»C-Pr P·P°C†C,PsC†PsPIC†PIP°C,Pë C-C₇PëPSPsC,P_μPeP°PS (PrPëPI. C₇PsP·PrC-P»Pë
B«P_μC₇PsC,PëPīPsPeP°P·P°PSPSCIB» C,P° B«PhC†PsP±P»PëIPsC†C,C-
P·P°C†C,PsC†C†PIP°PSPSCIB»).

P†PSC,,PsC₇PjP°C†C-C† C%PsPrPs P·P°C†C,PsC†C†PIP°PSPSC†
C-C₇PëPSPsC,P_μPeP°PSC† C† PePsPjP±C-PSP°C†C-C— P· C-PSC€PëPjPë
PīC₇P_μPīP°C₇P°C,P°PjPë PīP°C†C-C''PSC,P°Pj P· C†C₇P°P¶P_μPSPSC†PjPë
PīP_μC†C-PSPePë PIC-PrC†C†C,PSC†.

P_μP°C†C-C''PSC,Pë P· PīPsC₇C†C€P_μPSPSC†PjPë C,,C†PSPeC†C-C— PSPëC₇PsPe.

P—P°C†C,PsC†PsPIC†PIP°C,Pë P†C₇PëPSPsC,P_μPeP°PS P_HPjP°PeC†P° PīP°C†C-C''PSC,P°Pj
C-P· PīPsC₇C†C€P_μPSPSC†PjPë C,,C†PSPeC†C-C— PSPëC₇PsPe PSp_μ
C₇P_μPePsPjP_μPSPrC†C''C,CHC†C†, PsC†PeC-P»CHPePë PrPsC†P»C-PrP¶P_μPSPSC† C%PsPrPs
P·P°C†C,PsC†C†PIP°PSPSC† PīC₇P_μPīP°C₇P°C,C† C,P°PeC-PN₀ PeP°C,P_μPiPsC₇C-C—
PīP°C†C-C''PSC,C-PI PSp_μ PīC₇PsPIPsPrPëP»PsC†C† (PrPëPI. C₇PsP·PrC-P»Pë
B«P_μP°C₇PjP°PePsPeC-PSP_μC,PëPeP°B» C,P° B«PhC†PsP±P»PëIPsC†C,C-
P·P°C†C,PsC†C†PIP°PSPSC†B»).

P_μP°C†C-C''PSC,Pë P»C-C,PSC_HPsPiPs PIC-PeC†.

PŸPīP_μC†C-P°P»CH_HPSPëC... C,,P°C₇PjP°PePsPeC-PSP_μC,PëC†PSPëC...
PrPsC†P»C-PrP¶P_μPSC_H P·P° C†C†P°C†C,C_H PīP°C†C-C''PSC,C-PI P»C-C,PSC_HPsPiPs
PIC-PeC† PSp_μ PīC₇PsPIPsPrPëP»Pë. P'PsPrPSPsC†P°C†, PīP°C†C-C''PSC,P°Pj C†C-C''C—
PīC₇C†PīPë C†P»C-Pr C₇P_μC,P_μP»CH_HPSPs PīC-PrP±PëC₇P°C,Pë PrPsP·C†,
PsC†PeC-P»CHPePë C† PSPëC... PSP°P±P°PīP°C,Ps C†P°C†C,C-C€P_μ
PIPëC†PIP»C†C''C,CHC†C† P·PSPëP¶P_μPSPSC† P±C-PsP»PsPiC-C†PSPëC...
C,,C†PSPeC†C-PN₀. P_μP°C†C-C''PSC,Pë C†C-C''C— PīC₇C†PīPë PīPsC,C₇P_μP±C†C_HC,CH
P±C-P»CHC€ C-PSC,P_μPSC†PëPIPSPsPiPs C†PīPsC†C,P_μC₇P_μP¶P_μPSPSC† (PrPëPI.
C₇PsP·PrC-P» B«PhC†PsP±P»PëIPsC†C,C- P·P°C†C,PsC†C†PIP°PSPSC†B»).

P_μPsPrC-P±PSPs PrPs C-PSC€PëC... PīC₇PsC,PëPīC†C...P»PëPSPSPëC...
PīC₇P_μPīP°C₇P°C,C-PI, P†C₇PëPSPsC,P_μPeP°PS P_HPjP°PeC†P° C†P»C-Pr
PīPsC,C†PIP°C,Pë PrPs P·P°C†C,PsC†C†PIP°PSPSC† C,P° PīIPsPrPëC,Pë P·
PsP±P_μC₇P_μP¶PSC-C†C,C_H. P'PëPePsC₇PëC†C,P°PSPSC† P·P°C...PëC†PSPëC...
PsPeC†P»C†C₇C-PI, PjP°C†PePë C,P° C₇C†PeP°PIPëC†PsPe C''
PsP±PsPiB₇TM C†P·PePsPIPëPj.

Pj C₇P°P·C- PīPsC,C₇P°PīP»C†PSPSC† PePsPSC†P_μPSC,C₇P°C,C† P°P±Ps
C₇PsP·C†PëPSC† PrP»C† C-PSC,,C†P·C-C— PSP° C€PeC-C₇C† C†P»C-Pr
PSP_μPiP°PN₀PSPs P·PjPëC,Pë C₇PsP·C†PëPS C,P° C₇P_μC,P_μP»CH_HPSPs PIPëPjPëC,Pë
PjC-C†C†P_μ PePsPSC,P°PeC,C† PIPsPrPsC_H P· PjPëP»PsPj, P° C† C₇P°P·C-
PīPsC,C₇P°PīP»C†PSPSC† PSP° C†P»PëP·PsPIC- PsP±PsP»PsPSPePë B₇“ C†P»C-Pr
PSP_μPiP°PN₀PSPs P·PjPëC,Pë PIPsPrPsC_H.

PJC,PëP»C-P·P°C†C-CI.

PJC†C- PjP°C,PμC†C-P°P»Pë, C%Ps P·P°C†C,Psc†PspIC†C†C,CHC†C†C P†P»C†C
C†Psp·C†PëPSPμPSPSC†C C,P° PIPμP†PμPSPSC†C P†C†PμP†P°C†P°C,C†,
P†C-P†P»C†P†P°C†C,CH C†C,PëP»C-P·P°C†C-C— PIC-P†P†PspIC-P†PSPs P†Ps
C†C,P°PSP†P°C†C,PSPëC... P†C†PspC†PμP†C†C PjPμP†PëC†PSPsPiPs P·P°PëP»P°P†C†,
C%Ps P·P°C†C,Psc†PspIC†C†C,CHC†C†C P†Ps C†PëC,Psc,PspëC†PëC†PSPëC...
P†C†PμP†P°C†P°C,C-PI.

P''C-C,Pë.

PμC†PμP†P°C†P°C, P†C†PëP·PSP°C†PμPSPëPN P†P»C†C P·P°C†C,Psc†C†PIP°PSPSC†C
C,C-P»CHPëPë P†Psc†PspC†P»PëPjPë.

PμPμC†PμP†PsP·C¿PIP°PSPSC†C.

P†C†P»Pë Psc,C†PëPjP°PSC- P†PspIC-P†PspjP»PμPSPSC†C P†C†Psp P†PμC†PμP†Psp·C†PIP°PSPSC†C,
C%Ps PjPsp†Pμ PjP°C,Pë P»PμC,P°P»CHPSPëPN PSP°C†P»C-P†PspPë, P†C†Pë
P·P°C†C,Psc†C†PIP°PSPSC- P†Psp· P†C†PμP†P°C†P°C,C†, C%Ps P†C†PëP±P»PëP·PSPs
PIP†PIC-C†C- P†PμC†PμPIPëC%C†PIP°P»Pë C†PμPëPspjPμPSP†PspIP°PSC†
C,PμC†P°P†PμPIC,PëC†PSC† P†Psp·C†. P†P°PN±C-P»CHC€ P·PSP°C†C†C%PëPjPë
P†Psp±C-C†PSPëPjPë C†PμP°PëC†C-C†PjPë P±C†P»Pë PSPμPN,C†PspP†PμPSC-C†
C,C†P†PëPspPiPs C†C,C†P†PμPSC†C C,P° P†C-P°C†PμC†C C,C†P†PëPspPiPs C†C,C†P†PμPSC†C.
P†C-P†PspjPspPiPs P°PSC,PëP†Psc,C† P†Ps C-C†PëPSPsC,PμPëP°PSC† PSPμ C-C†PSC†C".
P†P»C-P† P†C†PspIPsP†PëC,Pë PjP°PëC†PëPjP°P»CHPSPs C-PSC,PμPSC†PëPIPSPμ
P†C-P†C,C†PëPjC†C†C†Pμ P»C-PëC†PIP°PSPSC†C, C%PsP± P·P°P†Psp±C-P†C,Pë
P·PSPμIPsP†PSPμPSPSC† PIPSP°C†P»C-P†PspPë P†C-P°C†PμC— C,P° PIPëP»C-PëC†PIP°C,Pë
PjPsp†P»PëPIC- C-PSC,,PμPëC†C-PN±PSC- C†C†PëP»P°P†PSPμPSPSC†C.

PμPsp±C-C†PSC- C†PμP°PëC†C-C—.

PμP»C-PSC-C†PSC- P†Psc†P»C-P†P†PμPSPSC†C.

P''P°PSC- C%PsP†Ps P†Psp±C-C†PSPëC... C†PμP°PëC†C-PN± P±C†P»Pë C†PμC,PμP»CHPSPs
P·C-P±C†P°PSC- C† P†C†PspC†PμC†C- P†Psc†P»C-P†P†PμPSC†C PjPμC,P°C†C,P°C,PëC†PSPsPiPs
PëPsp»Psc†PμPëC,P°P»CHPSPsPiPs C†P°PëC†, C†P°C†C,Psc,P° C—C... P†Psc†PIPë
PSP°PIPμP†PμPSP° PSPëP†C†Pμ. PμC†Pë P·P°C†C,Psc†C†PIP°PSPSC- P†C†PμP†P°C†P°C,C†
P†P»C†C C-PSC€PëC... P†PspPëP·P°PSC†, PspëC†C-Pj PëPsp»Psc†PμPëC,P°P»CHPSPsPiPs
C†P°PëC†, Psc†C-PëC†C" C,CHC†C†C PIPëPSPëPëPSPμPSPSC†C C†C...Psp†PëC...
P†Psp±C-C†PSPëC... C†PμP°PëC†C-PN±.

P†P°PN±P†Psc€PëC†PμPSC-C€PëPjPë (≥1/10) P†Psp·Psp»C-PjC-C,C†C†C†PëPjPë
P†Psp±C-C†PSPëPjPë C†PμP°PëC†C-C†PjPë C-C†PëPSPsC,PμPëP°PSC†C"

PIC-PrCfC,ChPsC+PμPSP° PrC-P°ChPμCΠ (PIPëPSPëPeP°C" P±C-P»CHC€Pμ PSC-P¶ C+PμChPμP· 24 PiPsPrPëPSPë PiC-CfP»CΠ PIPμPrPμPSPSCΠ PiChPμPiP°ChP°C,Cf) C,P° ChPsP·P»P°PrPë P· P±PsPeCf PeChPsPIC-, PIPeP»ChC+P°ChC+Pë PSPμPNëC,ChPsPiPμPSC-Ch, P°PSPμPjC-Ch C- C,ChPsPjP±PsCfPëC,PsPiPμPSC-Ch.

PkPμPNëC,ChPsPiPμPSC-CΠ C" PrPsP·PsP»C-PjC-C,CfChC+PëPj C,PsPeCfPëC+PSPëPj PμC,,PμPeC,PsPj. PkPμPNëC,ChPsPiPμPSC-CΠ PjP°P»P° PsP±PsChPsC,PSPëPNë C...P°ChP°PeC,PμCh C- PSPμ P±CfP»P° PeCfPjCfP»CΠC,PëPIPSsCh; PiC-Pr C+P°Cf PjPsPSPsC,PμChP°PiC-C— P°P±Ps PePsPjP±C-PSPsPIP°PSPsC— C,PμChP°PiC-C— CfPμChPμPrPSC-PNë C+P°Cf PrPs PrPsCfCΠPiPSPμPSPSCΠ PjC-PSC-PjP°P»CHPSPsPiPs ChC-PIPSCΠ PSPμPNëC,ChPsC,,C-P»C-PI CfC,P°PSPsPIPëPI 8 PrPSC-PI.

P"CfP¶Pμ C+P°CfC,Ps CfPiPsCfC,PμChC-PiP°PICfCΠ C,ChP°PSP·PëC,PsChPSPëPNë PiPsCfC,ChPëPNë C...PsP»C-PSPμChPiC-C+PSPëPNë CfPëPSPrChPsPj C,CΠP¶PePsPiPs CfC,CfPiPμPSCΠ.

PhCfPSPsPIPSPëPjPë PNëPsPiPs CfPëPjPiC,PsPjP°PjPë P±CfP»Pë ChP°PSPSCΠ PrC-P°ChPμCΠ C,P° ChC-P·PSC- C-PSC€C- CfPëPjPiC,PsPjPë, C,P°PeC- CΠPe P±C-P»CH Cf P¶PëPIPsC,C-, PiC-PrPIPëC%PμPSP° PiC-C,P»PëPIC-CfC,Ch, PjC-PsP· C- PiC-PrPIPëC%PμPSPμ CfP»PëPSPsPIPëPrC-P»PμPSPSCΠ, C%Ps PIPëPSPëPeP°P»Pë PiChPsC,CΠPiPsPj C-PSC,,CfP·C-C— C-ChPëPSPsC,PμPeP°PSCr P°P±Ps PIPiChPsPrPsPIP¶ PiPμChC€PëC... 24 PiPsPrPëPS PiC-CfP»CΠ C-PSC,,CfP·C-C—. PjC- CfPëPjPiC,PsPjPë P·PSPëPeP°P»Pë PiC-CfP»CΠ P·P°CfC,PsCfCfPIP°PSPSCΠ P°C,ChPsPiC-PSCr (PrPëPI. ChPsP·PrC-P» B«PhCfPsP±P»PëPIPsCfC,C- P·P°CfC,PsCfCfPIP°PSPSCΠB»).

PμPsPSPsC,PμChP°PiC-CΠ

PμChPs PiPμChPμP»C-C+PμPSC- PSPëP¶C+Pμ PiPsP±C-C+PSC- ChPμP°PeCfC-C—, ChPsP·CfC-PSPμPSC- CΠPe PjPsP¶P»PëPIPs P°P±Ps PNëPjPsPIC-ChPSPs PiPsPIB¶™ CΠP·P°PSC- C-P· P·P°CfC,PsCfCfPIP°PSPSCΠPj PiChPμPiP°ChP°C,Cf P†ChPëPSPsC,PμPeP°PS PhPjP°PeCfP°, PiPsPIC-PrPsPjP»CΠP»PsCfCΠ PrP»CΠ 765 PiP°CfC-C"PSC,C-PI, CΠPeC- PsC,ChPëPjCfPIP°P»Pë ChPμPePsPjPμPSPrPsPIP°PSCr PrPsP·Cf 350 PjPi/Pj² Cf PIPëPiP»CΠPrC- PjPsPSPsC,PμChP°PiC-C—. Pj PjPμP¶P°C... PePsP¶PSPsC— C+P°CfC,PsC,PSPsC— PiChCfPiPë PiPsP±C-C+PSC- ChPμP°PeCfC-C— PSP°PIPμPrPμPSC- Cf PiPsChCΠPrPeCf P·PjPμPSC€PμPSPSCΠ CfC,CfPiPμPSCΠ C,CΠP¶PePsCfC,C-. P§P°CfC,PsC,P° PiPsP±C-C+PSPëC... ChPμP°PeCfC-PNë PeP»P°CfPëC,,C-PeCfC"C,ChCfCΠ C,P°PePëPj C+PëPSPsPj: PrCfP¶Pμ C+P°CfC,Ps (≥1/10); C+P°CfC,Ps (PIC-Pr ≥1/100 PrPs <1/10); PSPμC+P°CfC,Ps (PIC-Pr ≥1/1000 PrPs <1/100); ChC-PrPePs (PIC-Pr ≥1/10000 PrPs <1/1000); PrCfP¶Pμ ChC-PrPePs (<1/10000); C+P°CfC,PsC,P° PSPμPIC-PrPsPjP° (PSPμ PjPsP¶Pμ P±CfC,Pë PsCfC-PSPμPSP° P· PSP°CΠIPSPëC... PrP°PSPëC...).

PμPsP±C-C+PSC- ChPμP°PeCfC-C—, PiChPs CΠPeC- PiPsPIC-PrPsPjP»CΠP»Pë PiC-Pr C+P°Cf PjPsPSPsC,PμChP°PiC-C— C-ChPëPSPsC,PμPeP°PSPsPj (P·P° CfC...PμPjPsCh 350 PjPi/Pj² PePsP¶PSC- 3 C,PëP¶PSC-)		
PμP»P°Cf CfPëCfC,PμPjPë PsChPiP°PSC-PI MedDRA	P§P°CfC,PsC,P°	PμPsP±C-C+PSP° ChPμP°PeCfC-CΠ
P†PSC,,PμPeCfC-C— C,P° C-PSPIP°P·C-C—	P§P°CfC,Ps	P†PSC,,PμPeCfC-C—

P— P±PsPeCf CÍPëCfC,PµPjPë PeCĤPsPIC- C,P° P»C-PjC,,P°C,PëC±PSPsC— CÍPëCfC,PµPjPë	P"CrP¶Pµ C±P°CfC,Ps	PkPµPNëC,CĤPsPiPµPSC-CĬ, P°PSPµPjC-CĬ
	P§P°CfC,Ps	PÿCĤPsPjP±PsC†PëC,PsPiPµPSC-CĬ, C,,PµP±CĤPëP»CHßPSP° PSPµPNëC,CĤPsPiPµPSC-CĬ
P— P±PsPeCf C,CĤP°PIP»PµPSPSCĬ C,P° PjPµC,P°P±PsP»C-P·PjCf	P"CrP¶Pµ C±P°CfC,Ps	P—PSPëP¶PµPSPSCĬ P°PiPµC,PëC,Cf
P— P±PsPeCf PSPµCĤPIPsPIPsC— CÍPëCfC,PµPjPë	P"CrP¶Pµ C±P°CfC,Ps	PfPsP»C-PSPµCĤPiC-C±PSPëPNë CÍPëPSPrCĤPsPj
P— P±PsPeCf CëP»CrPSPePsPIPs- PePëCëPePsPIPsPiPs C,CĤP°PeC,Cf	P"CrP¶Pµ C±P°CfC,Ps	P"C-P°CĤPµCĬ, P±P»CĤPIP°PSPSCĬ, PSCfPrPsC,P°, P±C-P»CHß Cf P¶PëPIPsC,C-
	P§P°CfC,Ps	P—P°PiPsCĤ
P— P±PsPeCf CëPeC-CĤPë C,P° PiC-PrCëPeC-CĤPSPsC— C,PeP°PSPëPSPë	P"CrP¶Pµ C±P°CfC,Ps	PĥP»PsPiPµC†C-CĬ (PsP±PsCĤPsC,PSP°)
P—P°PiP°P»CHßPSC- CĤPsP·P»P°PrPë C,P° CĤPµP°PeC†C-C— Cf PjC-CfC†C- PIPIPµPrPµPSPSCĬ C-PSBĤ™C"PeC†C-C—	P"CrP¶Pµ C±P°CfC,Ps	P—P°PiP°P»PµPSPSCĬ CÍP»PëP·PsPIPëC... PsP±PsP»PsPSPsPe, PiP°CĤCĬC±PeP°, P°CfC,PµPSC-CĬ
P·P°P±PsCĤP°C,PsCĤPSC- PrPsCfP»C-PrP¶PµPSPSCĬ	P§P°CfC,Ps	PµC-PrPIPëC%PµPSPSCĬ CĤC-PIPSCĬ PeCĤPµP°C,PëPSC-PSCf PI PeCĤPsPIC-, PiC-PrPIPëC%PµPSPSCĬ CĤC-PIPSCĬ C,CĤP°PSCfP°PjC-PSP°P· (PĥP·Pÿ C- PĥPÿPÿ), PiC-PrPIPëC%PµPSPSCĬ CĤC-PIPSCĬ P±C-P»C-CĤCfP±C-PSCf, PiC-PrPIPëC%PµPSPSCĬ CĤC-PIPSCĬ P»CfP¶PSPsC— C,,PsCfC,,P°C,P°P·Pë PI PeCĤPsPIC-

PĥPiPëCf PsPeCĤPµPjPëC... PiPsP±C-C±PSPëC... CĤPµP°PeC†C-PNë (PiCĤPë
PjPsPSPsC,PµCĤP°PiC-C—).

PÿCĬP¶PeP° PrC-P°CĤPµCĬ CÍPiPsCfC,PµCĤC-PiP°P»P°CfCĬ Cf 20 % PiP°C†C-C"PSC,C-PI,
CĬPeC- PrPsC,CĤPëPjCfPIP°P»PëCfCĬ CĤPµPePsPjPµPSPrP°C†C-PNë P· PePsPSC,CĤPsP»CĤ
PrC-P°CĤPµC—. PJ C†PëPeP»P°C... C,PµCĤP°PiC-C—, C%Ps PiC-PrP»CĬPiP°P»Pë
PsC†C-PSCĤPIP°PSPSCĤ, C,CĬP¶PeP° PrC-P°CĤPµCĬ CÍPiPsCfC,PµCĤC-PiP°P»P°CfCĬ Cf
14 %. PÿPµCĤPµPrPSC-PNë C±P°Cf PrPs PiPsCĬPIPë CĤC-PrPePëC... PIPëPiPsCĤPsP¶PSPµPSCĤ
PiC-CÍP»CĬ C-PSC,,CfP·C-C— C-CĤPëPSPsC,PµPeP°PSCf CÍC,P°PSPsPIPëPI 5 PrPSC-PI.

PkCzPrPsC,P° C- P±P»CĤPIP°PSPSCĬ PjP°P»Pë C,CĬP¶PePëPNë PiPµCĤPµP±C-Pi Cf
PiCĤPëP±P»PëP·PSPs 10 % PiP°C†C-C"PSC,C-PI, CĬPeC- PsC,CĤPëPjCfPIP°P»Pë
PiCĤPsC,PëP±P»CĤPIP°P»CHßPSC- PiCĤPµPiP°CĤP°C,Pë.

P—P°PiPsCĤ CÍPiPsCfC,PµCĤC-PiP°PICfCĬ Cf PjPµPSCë PSC-P¶ 10 % PiP°C†C-C"PSC,C-PI.

PkPµPNëC,CĤPsPiPµPSC-CĬ CÍPiPsCfC,PµCĤC-PiP°P»P°CfCĬ Cf 78,7 % PiP°C†C-C"PSC,C-PI,
CÍPµCĤPµPr CĬPePëC... C,CĬP¶PePëPNë CÍC,CfPiC-PSCĤ PiPµCĤPµP±C-PiCf
(PeC-P»CHßPeC-CfC,CHß PSPµPNëC,CĤPsC,,C-P»C-PI <500 PeP»C-C,PëPS/PjPj³)
CÍPiPsCfC,PµCĤC-PiP°PICfCĬ Cf 22,6 % PiP°C†C-C"PSC,C-PI. PJ C†PëPeP»P°C...
C,PµCĤP°PiC-C—, C%Ps PiC-PrP»CĬPiP°P»Pë PsC†C-PSCĤPIP°PSPSCĤ, Cf 18 %
PeC-P»CHßPeC-CfC,CHß PSPµPNëC,CĤPsC,,C-P»C-PI P±CfP»P° PjPµPSCëPµ

1000 PeP»C-C,PëPS/PjPj³, PIPeP»CĤC†P°CĤC†Pë 7,6 % P· PeC-P»CHĤPeC-CĤC,CĤ
PSPμPNëC,CĤPsC,,C-P»C-PI <500 PeP»C-C,PëPS/PjPj³. PμPsPIPSPμ PIC-PrPSPsPIP»PμPSPSCĬ
PĭPsPeP°P·PSPëPeC-PI P·P°P·PIPëC†P°PNë C,CĤPëPIP°P»Ps PrPs 22 PrPSC-PI.

P°P°CĤCĬC†PeP° P· PSPμPNëC,CĤPsPiPμPSC-C°CĤ C,CĬP¶PePsPiPs CĤC,CžPiPμPSCĬ
CĤPiPsCĤC,PμCĤC-PiP°P»P°CĤCĬ Cr 6,2 % PiP°C†C-C°PSC,C-PI C,P° 1,7 % PICĤC-C...
C†PëPeP»C-PI C,PμCĤP°PiC-C—.

P·PiC-P·PsPrPë C-PSC,,PμPeC†C-PNë C,CĤP°PiP»CĬP»PëCĤCĬ PiCĤPëP±P»PëP·PSPs Cr 10,3 %
PiP°C†C-C°PSC,C-PI (2,5 % PICĤC-C... C†PëPeP»C-PI C,PμCĤP°PiC-C—) C,P° P±CrP»Pë
PiPsPiBĤ™ CĬP·P°PSC- P· C,CĬP¶PePsCĤ PSPμPNëC,CĤPsPiPμPSC-C°CĤ PiCĤPëP±P»PëP·PSPs Cr
5,3 % PiP°C†C-C°PSC,C-PI (1,1 % PICĤC-C... C†PëPeP»C-PI C,PμCĤP°PiC-C—); Cr
PrPIPsC... PIPëPiP°PrPeP°C... C†Pμ CrCĤPeP»P°PrPSPμPSPSCĬ PiCĤPëP·PIPμP»Ps PrPs
P»PμC,P°P»CHĤPSPsPiPs PSP°CĤP»C-PrPeCĤ.

PμCĤPs P°PSPμPjC-CĤ PiPsPIC-PrPsPjP»CĬP»Pë PiCĤPëP±P»PëP·PSPs Cr 58,7 %
PiP°C†C-C°PSC,C-PI (8 % C-P· CĤC-PIPSμPj PiPμPjPsPiP»PsP±C-PSCr <8 Pi/PrP» C,P° 0,9 %
C-P· CĤC-PIPSμPj PiPμPjPsPiP»PsP±C-PSCr <6,5 Pi/PrP»).

PjCĤPsPjP±PsC†PëC,PsiPiPμPSC-CĬ (<100000 PeP»C-C,PëPS/PjPj³)
CĤPiPsCĤC,PμCĤC-PiP°P»P°CĤCĬ Cr 7,4 % PiP°C†C-C°PSC,C-PI (1,8 % PICĤC-C...
C†PëPeP»C-PI C,PμCĤP°PiC-C—), CĤPμCĤPμPr CĬPePëC... Cr 0,9 % PiP°C†C-C°PSC,C-PI
(0,2 % C†PëPeP»C-PI C,PμCĤP°PiC-C—) PeC-P»CHĤPeC-CĤC,CĤ
C,CĤPsPjP±PsC†PëC,C-PI P±CrP»P° PSP° CĤC-PIPS- £50000 PeP»C-C,PëPS/PjPj³. Pj
PjP°PNëP¶Pμ PICĤC-C... PiP°C†C-C°PSC,C-PI PIC-PrPSPsPIP»PμPSPSCĬ
PĭPsPeP°P·PSPëPeC-PI C,CĤPëPIP°P»Ps PrPs 22 PrPSC-PI.

P°P°CĤC,CĤPëPNë C...PsP»C-PSPμCĤPiC-C†PSPëPNë CĤPëPSPrCĤPsPj.

PjCĤP°PSP·PëC,PsiCĤPSPëPNë PiPsCĤC,CĤPëPNë C...PsP»C-PSPμCĤPiC-C†PSPëPNë
CĤPëPSPrCĤPsPj C,CĬP¶PePsPiPs CĤC,CĤPiPμPSCĬ CĤPiPsCĤC,PμCĤC-PiP°PICĤCĬ Cr 9 %
PiP°C†C-C°PSC,C-PI, CĬPeC- PsC,CĤPëPjCrPIP°P»Pë PjPsPSPsC,PμCĤP°PiC-CĤ.

PĤCĤC,PμPSC-CĬ PjP°P»P° C,CĬP¶PePëPNë PiPμCĤPμP±C-Pi Cr PjPμPSC€Pμ 10 %
PiP°C†C-C°PSC,C-PI, CĬPeC- PsC,CĤPëPjCrPIP°P»Pë PjPsPSPsC,PμCĤP°PiC-CĤ.
PμCĤPëC†PëPSPSPs-PSP°CĤP»C-PrPePsPIPëPNë P·PiBĤ™ CĬP·PsPe PjC-P¶ C†PëPj CĬPIPëC%PμPj
C,P° P·P°CĤC,PsiCĤCrPIP°PSPSCĬPj C-CĤPëPSPsC,PμPeP°PSCr PSPμ P±CrPI C†C-C,PePs
PICĤC,P°PSPsPIP»PμPSPëPNë. P°P°CĤCĬC†PeP° Cr CĤP°P·C- PIC-PrCĤCĤC,PSPsCĤC,C-
C-PSC,,PμPeC†C-C— P°P±Ps CĤCĤPiCĤC,PsiCĤPsC— C,CĬP¶PePsC— PSPμPNëC,CĤPsPiPμPSC-C—
C,CĤP°PiP»CĬP»P°CĤCĬ Cr 12 % PiP°C†C-C°PSC,C-PI, CĬPeC- PsC,CĤPëPjCrPIP°P»Pë
PjPsPSPsC,PμCĤP°PiC-CĤ.

P>P°P±PsCĤP°C,PsiCĤPSC- PiPsPeP°P·PSPëPePë

PĤPμPIPμP»PëPePμ P°P±Ps PiPsPjC-CĤPSPμ C,CĤP°PSP·PëC,PsiCĤPSPμ PiC-PrPIPëC%PμPSPSCĬ
CĤPëCĤPsPIP°C,PePsPIPëC... CĤC-PIPS-PI C,CĤP°PSCĤP°PjC-PSP°P·, P»CrP¶PSPsC—
C,,PsiCĤC,,P°C,P°P·Pë C†Pë P±C-P»C-CĤCĤP±C-PSCr CĤPiPsCĤC,PμCĤC-PiP°P»PsCĤCĬ Cr 9,2 %,
8,1 % C,P° 1,8 % PiP°C†C-C°PSC,C-PI PIC-PrPiPsPIC-PrPSPs Cr CĤP°P·C-
PIC-PrCĤCĤC,PSPsCĤC,C- PiCĤPsPiCĤPμCĤCĤC†PëC... PjPμC,P°CĤC,P°P·C-PI Cr
PiPμC†C-PSC†C-. PĤPμPIPμP»PëPePμ P°P±Ps PiPsPjC-CĤPSPμ C,CĤP°PSP·PëC,PsiCĤPSPμ
PiC-PrPIPëC%PμPSPSCĬ CĤC-PIPSĬ CĤPëCĤPsPIP°C,PePsPIPsiPs PeCĤPμP°C,PëPSC-PSCr
CĤPiPsCĤC,PμCĤC-PiP°P»PsCĤCĬ Cr 7,3 % PiP°C†C-C°PSC,C-PI.

PeP°PiPμC†PëC,P°P±C-PSPsPj.

PšP°CÍC,Ps, PiPsP±C-C†PSC- CĤPμP°PeC†C-C— III C,P° IV CÍC,CžPiPμPSC-PI:

PSPμPNëC,CĤPsPiPμPSC-CĬ, C,CĤPsPjP±PsP/PμPjP±PsP»C-CĬ, P°CĤC,PμCĤC-P°P»CHbPSP°
PiC-PiPμCĤC,PμPSP·C-CĬ, C-CëPμPjC-CĬ/C-PSC,,P°CĤPeC, PjC-PsPeP°CĤPrP°.

PμPsPIPSP° C-PSC,,PsCĤPjP°C†C-CĬ PiCĤPs PiPsP±C-C†PSC- CĤPμP°PeC†C-C—
PeP°PiPμC†PëC,P°P±C-PSCr C,P° P±PμPIP°C†PëP·C†PjP°P±C† PSP°PIPμPrPμPSP° PI
C-PSCÍC,CĤC†PeC†C-C— PrP»CĬ PjPμPrPëC†PSPsPiPs P·P°CÍC,PsCÍC†PIP°PSPSCĬ
C†PëC... P»C-PeP°CĤCÍCHbPePëC... P·P°CÍPsP±C-PI.

P PsP·PIPëC,PsPe P°CĤC,PμCĤC-P°P»CHbPSPsC— PiC-PiPμCĤC,PμPSP·C-C— III CÍC,C†PiPμPSCĬ
P±C†PI PsCÍPSPsPIPSPëPj CÍC†C,C,C”PIPëPj CĤPëP·PëPePsPj, PiPsPIbĤ™ CĬP·P°PSPëPj C-P·
PrPsPrP°PIP°PSPSCĬPj P±PμPIP°C†PëP·C†PjP°P±C† PrPs P±PsP»CHCÍPSPsC— PrPsP·Pë
PiCĤPμPiP°CĤP°C,C-PI C-CĤPëPSPsC,PμPeP°PS/5-PαPJ/PαPĤ. PĤCĤC-Pj C,PsPiPs, PiCĤPë
P·P°CÍC,PsCÍC†PIP°PSPSC- C†C-C”C— CÍC...PμPjPë P»C-PeC†PIP°PSPSCĬ
CÍPiPsCÍC,PμCĤC-PiP°P»PsCÍCĬ PSPμPIPμP»PëPePμ P·CĤPsCÍC,P°PSPSCĬ C†P°CÍC,PsC,Pë
PiPsP±C-C†PSPëC... CĤPμP°PeC†C-PNë C...C-PjC-PsC,PμCĤP°PiC-C— III/IV CÍC,C†PiPμPSCĬ bĤ“
PrC-P°CĤPμC— C,P° P»PμPNëPePsPiPμPSC-C—, PiPsCĤC-PIPSCĬPSPs P· PiP°C†C-C”PSC,P°PjPë,
CĬPeC- PsC,CĤPëPjC†PIP°P»Pë C,C-P»CHbPePë P±PsP»CHCÍPSCr PrPsP·C†
C-CĤPëPSPsC,PμPeP°PS/5-PαPJ/PαPĤ. P†PSCëP° C-PSC,,PsCĤPjP°C†C-CĬ PiCĤPs
PiPsP±C-C†PSC- CĤPμP°PeC†C-C— PePsPjP±C-PSPsPIP°PSPsC— C,PμCĤP°PiC-C— P·
P±PμPIP°C†PëP·C†PjP°P±PsPj PSP°PIPμPrPμPSP° PI C-PSCÍC,CĤC†PeC†C-C— PrP»CĬ
PjPμPrPëC†PSPsPiPs P·P°CÍC,PsCÍC†PIP°PSPSCĬ C†CHbPsPiPs P»C-PeP°CĤCÍCHbPePsPiPs
P·P°CÍPsP±C†.

P·C†P»Pë PiCĤPsPIPμPrPμPSC- PrPsCÍP»C-PrP¶PμPSPSCĬ P·P°CÍC,PsCÍC†PIP°PSPSCĬ
C-CĤPëPSPsC,PμPeP°PSCr C† PePsPjP±C-PSP°C†C-C— P· 5-PαPJ C,P° PαPĤ PrP»CĬ
P»C-PeC†PIP°PSPSCĬ PjPμC,P°CÍC,P°C,PëC†PSPsPiPs PePsP»PsCĤPμPeC,P°P»CHbPSPsPiPs
CĤP°PeC†.

P”P°PSC- P±PμP·PiPμPePë C%PsPrPs PiPsP±C-C†PSPëC... CĤPμP°PeC†C-PNë,
PsC,CĤPëPjP°PSC- C† PiCĤPsC†PμCÍC- PeP»C-PSC-C†PSPëC... PrPsCÍP»C-PrP¶PμPSCĤb,
PiPsPeP°P·C†CHC,CHb, C%Ps PrC†P¶Pμ C†P°CÍC,Ps
CÍPiPsCÍC,PμCĤC-PiP°CHC,CHbCÍCĬ PiPsP±C-C†PSC- CĤPμP°PeC†C-C— III P°P±Ps
IV CÍC,C†PiPμPSCĬ P·P° CëPeP°P»PsCH PkP°C†C-PsPSP°P»CHbPSPsPiPs
C-PSCÍC,PëC,C†C,C† CĤP°PeC†, CĬPeC-, PjPsP¶P»PëPIPs P°P±Ps PNëPjPsPIC-CĤPSPs,
PiPsPIbĤ™ CĬP·P°PSC- C-P· P·P°CÍC,PsCÍC†PIP°PSPSCĬPj C,PμCĤP°PiC-C—, P·
P±PsPeC† C,P°PePëC... PeP»P°CÍC-PI CÍPëCÍC,PμPj PsCĤPiP°PSC-PI: PeCĤPsPI C,P°
P»C-PjC,,P°C,PëC†PSP° CÍPëCÍC,PμPjP°, CëP»C†PSPePsPIPs-PePëCëPePsPIPëPNë
C,CĤP°PeC,, CëPeC-CĤP° C,P° PiC-PrCëPeC-CĤPSP° C,PeP°PSPëPSP°.

P”P°P»C- PSP°PIPμPrPμPSC- PiPsP±C-C†PSC- CĤPμP°PeC†C-C—, C%Ps, PjPsP¶P»PëPIPs P°P±Ps
B PNëPjPsPIC-CĤPSPs, P±C†P»Pë PiPsPIbĤ™ CĬP·P°PSC- C-P· P·P°CÍC,PsCÍC†PIP°PSPSCĬPj
C-CĤPëPSPsC,PμPeP°PSCr C- PiCĤPs CĬPeC- PiPsPIC-PrPsPjP»CĬP»Pë C†
145 PiP°C†C-C”PSC,C-PI, CĬPeC- PsC,CĤPëPjC†PIP°P»Pë C-CĤPëPSPsC,PμPeP°PS C†
CĤPμPePsPjPμPSPPrPsPIP°PSC-PNë PrPsP·C- 180 PjPi/Pj² C† PePsPjP±C-PSPsPIP°PSC-PNë
C,PμCĤP°PiC-C— P· 5-PαPJ/PαPĤ PePsP¶PSC- 2 C,PëP¶PSC-.

P _μ PsP±C-C±PSC- C ₇ P _μ P°PeC†C-C—, P _i C ₇ Ps C ₁ PeC- P _i PsPIC-PrPsPjP»C ₁ P»Pë P _i C-Pr C±P°C ₁ PePsPjP±C-PSPsPIP°PSPsC— C,P _μ C ₇ P°P _i C-C— P· C-C ₇ PëPSPsC,P _μ PeP°PSPsPj (P·P°C ₁ C...P _μ PjPsC ₇ 180 PjPi/Pj ² PePsP ₁ PSC- 2 C,PëP ₁ PSC-)		
P ₇ P»P°C ₁ C ₁ PëC ₁ C,P _μ PjPë PsC ₇ PiP°PSC-PI MedDRA	P ₇ P°C ₁ C,P ₇ S,C,P°	P _μ PsP±C-C±PSP° C ₇ P _μ P°PeC†C-C ₁
P†PSC,,P _μ PeC†C-C— C,P° C-PSIPiP°P·C-C—	P ₇ P°C ₁ C,P ₇ S	P†PSC,,P _μ PeC†C-C—
P— P±PsPeC ₁ C ₁ PëC ₁ C,P _μ PjPë PeC ₇ PsPIC- C,P° P»C-PjC,,P°C,PëC±PSPsC— C ₁ PëC ₁ C,P _μ PjPë	P°C ₁ P ₁ P _μ C±P°C ₁ C,P ₇ S	P ₇ C ₇ PsPjP±PsC†PëC,P ₇ PiP _μ PSC-C ₁ , PSP _μ PNëC,C ₇ PsPiP _μ PSC-C ₁ , P°PSP _μ PjC-C ₁
	P ₇ P°C ₁ C,P ₇ S	P ₇ P _μ P±C ₇ PëP»C ₇ HPSP° PSP _μ PNëC,C ₇ PsPiP _μ PSC-C ₁
P— P±PsPeC ₁ C,C ₇ P°PIP»P _μ PSPSC ₁ C,P° PjP _μ C,P°P±PsP»C-P·PjC ₁	P°C ₁ P ₁ P _μ C±P°C ₁ C,P ₇ S	P—PSPëP ₁ P _μ PSPSC ₁ P°PiP _μ C,PëC,C ₁
P— P±PsPeC ₁ PSP _μ C ₇ PIPsPIPsC— C ₁ PëC ₁ C,P _μ PjPë	P°C ₁ P ₁ P _μ C±P°C ₁ C,P ₇ S	P ₁ PsP»C-PSP _μ C ₇ PiC-C±PSPëPNë C ₁ PëPSP ₁ C ₇ PsPj
P— P±PsPeC ₁ CëP»C ₁ PSPePsPIPs-PePëCëPePsPIPsPiPs C,C ₇ P°PeC,C ₁	P°C ₁ P ₁ P _μ C±P°C ₁ C,P ₇ S	P°C-P°C ₇ P _μ C ₁ , P±P»C ₇ PIP°PSPSC ₁ , PSC ₁ PrPsC,P°
	P ₇ P°C ₁ C,P ₇ S	P°C-P»C ₇ C ₁ P ₁ PëPIPsC,C-, P·P°PiPsC ₇
P— P±PsPeC ₁ CëPeC-C ₇ Pë C,P° P _i C-PrCëPeC-C ₇ PSPsC— C,PeP°PSPëPSPë	P°C ₁ P ₁ P _μ C±P°C ₁ C,P ₇ S	P ₇ P»PsPiP _μ C†C-C ₁ (PsP±PsC ₇ PsC,PSP°)
P—P°PiP°P»C ₇ HPSC- C ₇ PsP·P»P°PrPë C,P° C ₇ P _μ P°PeC†C-C— C ₁ PjC-C ₁ C†C-PIPIP _μ PrP _μ PSPSC ₁ C-PSB ₇ ™C°PeC†C-C—	P°C ₁ P ₁ P _μ C±P°C ₁ C,P ₇ S	P—P°PiP°P»P _μ PSPSC ₁ C ₁ P»PëP·PsPIPëC... PsP±PsP»PsPSPsPe, P°C ₁ C,P _μ PSC-C ₁
	P ₇ P°C ₁ C,P ₇ S	P°P°C ₇ C ₁ C±PeP°
P·P°P±PsC ₇ P°C,P ₇ C ₇ PSC-PrPsC ₁ P»C-PrP ₁ P _μ PSPSC ₁	P°C ₁ P ₁ P _μ C±P°C ₁ C,P ₇ S	P _μ C-PrPIPëC%P _μ PSPSC ₁ C ₇ C-PIPsC ₁ C,C ₇ P°PSC ₁ P°PjC-PSP°P· (P ₇ P·P ₇ C-P ₇ P ₇ P ₇), P _i C-PrPIPëC%P _μ PSPSC ₁ C ₇ C-PIPsC ₁ P±C-P»C-C ₇ C ₁ P±C-PSC ₁ , P _i C-PrPIPëC%P _μ PSPSC ₁ C ₇ C-PIPsC ₁ P»C ₁ P ₁ PSPsC— C,,PsC ₁ C,,P°C,P°P·Pë PI PeC ₇ PsPIC-

P₇PiPëC₁ PsPeC₇P_μPjPëC... P_iPsP±C-C±PSPëC... C₇P_μP°PeC†C-PNë (P_iC₇Pë PePsPjP±C-PSPsPIP°PSC-PNë C,P_μC₇P°P_iC-C—).

P₇C₁P₁P_μPeP° PrC-P°C₇P_μC₁ C₁PiPsC₁C,P_μC₇C-PiP°P»P°C₁C₁ C₁ 13,1 % P_iP°C†C-C°PSC,C-PI, C₁PeC- PrPsC,C₇PëPjC₁PIP°P»PëC₁C₁ C₇P_μPePsPjP_μPSP₁P°C†C-PNë P· PePsPSC,C₇PsP»C₇ PrC-P°C₇P_μC—. Pj C†PëPeP»P°C... C,P_μC₇P°P_iC-C—, C%Ps P_iC-PrP»C₁PiP°P»Pë PsC†C-PSC₇PIP°PSPSC₇, C,C₁P₁PeP° PrC-P°C₇P_μC₁ C₁PiPsC₁C,P_μC₇C-PiP°P»P°C₁C₁ C₁ 3,9 %.

P₇C₁PrPsC,P° C- P±P»C₇PIP°PSPSC₁ C,C₁P₁PePsPiPs C₁C,C₁PiP_μPSC₁ C₁PiPsC₁C,P_μC₇C-PiP°P»PëC₁C₁ P· PSPëP₁C±PsC₇ C±P°C₁C,P₇S,P₇C₇ (C₁ 2,1 % C,P° 2,8 % P_iP°C†C-C°PSC,C-PI PIC-PrPiPsPIC-PrPSPs).

P—P°PiPsC₇ PIPSP°C₁P»C-PrPsPe P·P°C₁C,P₇C₁C₁PIP°PSPSC₁ C-C₇PëPSPsC,P_μPeP°PSC₁ C,P°/P°P±Ps P»PsPiP_μC₇P°PjC-PrC₁ C₁PiPsC₁C,P_μC₇C-PiP°PIC₁C₁ C₁ 3,4 % P_iP°C†C-C°PSC,C-PI.

P₇P_μPNëC,C₇PsPiP_μPSC-C₁ C₁PiPsC₁C,P_μC₇C-PiP°P»P°C₁C₁ C₁ 82,5 % P_iP°C†C-C°PSC,C-PI,

C,,PsCfC,,P°C,P°P·Pë P°P±Ps P±C-P»C-CfCfP±C-PSCf CfPïPsCfC,PµCfC-PiP°P»PsCfCf Cf
15 %, 11 %, 11 % C,P° 10 % PiP°C†C-C"PSC,C-PI PIC-PrPiPsPIC-PrPSPs Cf CfP°P·C-
PIC-PrCfCfC,PSPsCfC,C- PiCfPsPiCfPµCfCfCfC±PëC... PjPµC,P°CfC,P°P·C-PI Cf
PiPµC±C-PSC†C-. PÿCfP°PSP·PëC,PscfPSPµ PiC-PrPiPëC%PµPSPSCf CfC-PIPS-C-PI C†PëC...
PiPsPeP°P·PSPëPeC-PI III CfC,CfPiPµPSCf C,CfP¶PePsCfC,C- CfPiPsCfC,PµCfC-PiP°P»PsCfCf
Cf 0 %, 0 %, 0 % C,P° 1 % PiP°C†C-C"PSC,C-PI PIC-PrPiPsPIC-PrPSPs. P'PëPiP°PrPeC-PI
IV CfC,CfPiPµPSCf C,CfP¶PePsCfC,C- PrP°PSPsC— PiPsP±C-C±PSPsC— CfPµP°PeC†C-C—
PSPµ CfPiPsCfC,PµCfC-PiP°P»PsCfCf.

P"CrP¶Pµ CfC-PrPePs PSP°PrC...PsPrPëP»Pë PiPsPIC-PrPsPjP»PµPSPSCf PiCfPs
PiC-PrPiPëC%PµPSPSCf CfC-PIPS-C-PI P°PjC-P»P°P·Pë C,P°/P°P±Ps P»C-PiP°P·Pë.

PµPsPIC-PrPsPjP»CfP»Pë PiCfPs CfC-PrPeC-CfPSC- PIPëPiP°PrPePë
PiC-PiPsPeP°P»C-C"PjC-C— C,P° PiC-PiPsPSP°C,CfC-C"PjC-C—, PiPsCfPIP° CfPePëC...
P±CfP»P° PiPµCfPµPiP°P¶PSPs PiPsPiBf™ CfP·P°PSP° P· PrC-P°CfPµC"Cf C-
P±P»CfPIP°PSPSCfPj.

P†PSC€C- PiPsP±C-C±PSC- CfPµP°PeC†C-C—, PiCfPs CfPeC- PiPsPIC-PrPsPjP»CfP»Pë Cf
PeP»C-PSC-C±PSPëC... PrPsCfP»C-PrP¶PµPSPSCfC... P·P°CfC,PscfCfPiP°PSPSCf
C-CfPëPSPsC,PµPeP°PSCf P·P° CfC...PµPjPsCf 1 CfP°P· PSP° C,PëP¶PrPµPSCf.

Pj PeP»C-PSC-C±PSPëC... PrPsCfP»C-PrP¶PµPSPSCfC... P·P°CfC,PscfCfPiP°PSPSCf
C-CfPëPSPsC,PµPeP°PSCf PiPsPIC-PrPsPjP»CfP»Pë PiCfPs PSP°CfC,CfPiPSC- PiPsP±C-C±PSC-
CfPµP°PeC†C-C—, PiPsPiBf™ CfP·P°PSC- C-P· P·P°CfC,PscfCfPiP°PSPSCfPj
PiCfPµPiP°CfP°C,Cf: P±C-P»Cf, CfPµPiCfPëCf, CfPsP·P»P°PrPë P· P±PsPeCf PiCfCfPjPsC—
PePëC€PePë, PeP°PSPPrPëPrPsPjC-PePsP· C€P»CfPSPePsPIPs-PePëC€PePsPIPsPiPs C,CfP°PeC,Cf,
PiC-PiPsPjP°PiPSC-C"PjC-Cf, PIPëCfPëPiP°PSPSCf, CfPëPjPiC,PsPjPë P· P±PsPeCf
C€PeC-CfPë, PiPsCfCfC€PµPSPSCf C...PsPrPë, CfPiP»CfC,P°PSC-CfC,Cf
CfPIC-PrPsPjPsCfC,C-, PiPsP»PsPIPSPëPNë P±C-P»Cf, PSPµPiCfPëC,PsPjPSC-CfC,Cf,
PiCfPëPiP»PëPIPë, P±CfP°PrPëPeP°CfPrC-Cf, C-PSC,,PµPeC†C-C—
CfPµC±PsPIPëPIC-PrPSPëC... C€P»CfC...C-PI, P±C-P»Cf Cf PiCfCfPrCfC...,
PiC-PrPiPëC%PµPSPSCf PiP°PjPjP°PiP»CfC,P°PjC-P»C,CfP°PSCfC,,PµCfP°P·Pë,
PeCfPsPIPsPIPëP»PëPIPë, CfPëPSPrCfPsPj P»C-P·PëCfCf PiCfC...P»PëPSPë, CfPµCfC†PµPIPs-
CfCfPrPëPSPSC- P·P°C...PIPsCfCfPIP°PSPSCf (CfC,PµPSPsPeP°CfPrC-Cf, P·CfPiPëPSPeP°
CfPµCfC†Cf, C-PSC,,P°CfPeC, PjC-PsPeP°CfPrP°, C-C€PµPjC-Cf PjC-PsPeP°CfPrP°,
CfPsP·P»P°PrPë P· P±PsPeCf PiPµCfPëC,,PµCfPëC±PSPëC... CfCfPrPëPS, CfCfPrPëPSPSC-
P·P°C...PIPsCfCfPIP°PSPSCf) C- C,CfPsPjP±PsPµPjP±PsP»C-C±PSC- CfPIPëC%P°
(P°CfC,PµCfC-P°P»CfPSPëPNë C,CfPsPjP±PsP·, C-C€PµPjC-C±PSPëPNë C-PSCfCfP»CfC,,
PiPsCfCfC€PµPSPSCf PjPsP·PePsPIPsPiPs PeCfPsPIPsPsP±C-PiCf, PiP»PëP±PsPePëPNë
C,CfPsPjP±PsC,,P»PµP±C-C,, PµPjP±PsP»C-Cf CfCfPrPëPS PSPëP¶PSCfPsC—
PeC-PSC†C-PIPePë, P»PµPiPµPSPµPiP° PµPjP±PsP»C-Cf, C,CfPsPjP±PsC,,P»PµP±C-C,,
C,CfPsPjP±PsP· C- CfP°PiC,PsPIPëPNë P»PµC,P°P»CfPSPëPNë PSP°CfP»C-PrPsPe) (PrPëPI.
CfPsP·PrC-P» B«PhCfPsP±P»PëPIPsCfC,C- P·P°CfC,PscfCfPiP°PSPSCfB»).

PµC-CfP»CfCfPµC"CfC,CfP°C†C-PNëPSPµ CfPiPsCfC,PµCfPµP¶PµPSPSCf.

PfP°CfC,Psc,P° PIPëPSPëPePSPµPSPSCf PiPsP±C-C±PSPëC... CfPµP°PeC†C-PNë Cf
PiPµCfC-PsPrC- PiC-CfP»CfCfPµC"CfC,CfP°C†C-PNëPSPsPiPs
CfPiPsCfC,PµCfPµP¶PµPSPSCf PSPµPIC-PrPsPjP° (PSPµPjPsP¶P»PëPIPs PICfC,P°PSPsPIPëC,Pë
PSP° PsCfPSPsPIC- C-CfPSCfCfC±PëC... PrP°PSPëC...).

[illegible]

P— P±PsPeCf C€P»CfPSPePsPIPs- PeP€C€PePsPIPsPiPs C,ChP°PeC,Cf	PљP€C€PePsPIP° PSPµPiCћPsC...C-PrPSC-CfC,Ch; C-P»PµCfCf: C,P°PePsP¶ PiPsPIC-PrPsPjP»C¶P»P€ PiCћPs PIP€PiP°PrPeP€ C-P»PµCfCfCf P±PµP· PiPsPiPµCћPµPrPSCћPsPiPs PIP€PSP€PePSPµPSPSC¶ PePsP»C-C,Cf; PjPµPiP°PePsP»PsPS; C€P»CfPSPePsPIPs- PeP€C€PePsPIP€PNё PeCћPsPIPsPIP€P»P€PI; PePsP»C-C,, PI PsPeCћPµPjP€C... PIP€PiP°PrPeP°C... PePsP»C-C, P±CfPI CfCfPeP»P°PrPSPµPSP€PNё PIP€CћP°P·PeP°PjP€, PeCћPsPIPsC,PµC†PµCћ, C-P»PµCfCfPsPj P°P±Ps C-PSC,,PµPeC†C-C”Cћ; C,P€C,,P»C-C,; C-C€PµPjC-C†PSP€PNё PePsP»C-C,; PIP€CћP°P·PePsPIP€PNё PePsP»C-C,; C€P»CfPSPePsPIPs-PeP€C€PePsPIP° PeCћPsPIPsC,PµC†P°; CfP€PjPiC,PsPjP°C,P€C†PSPµ P°P±Ps P±PµP·CfP€PjPiC,PsPjPSPµ PiC-PrPIP€C%PµPSPSC¶ CћC-PIPS¶ C,,PµCћPjPµPSC,C-PI PiC-PrC€P»CfPSPePsPIPsC— P·P°P»PsP·P€; PiPµCћC,,PsCћP°C†C-C¶ PeP€C€PµC†PSP€PeCf
P— P±PsPeCf C€PeC-CћP€ C,P° PiC-PrC€PeC-CћPSPsC— C,PeP°PSP€PSP€	P€PeC-CћPSC- CћPµP°PeC†C-C—
P—P°PiP°P»CHPSC- CћPsP·P»P°PrP€ C,P° CћPµP°PeC†C-C— Cf PjC-CfC†C- PIPIPµPrPµPSPSC¶ C-PSбћ™C”PeC†C-C—	P PµP°PeC†C-C— Cf PjC-CfC†C- C-PSC,,CfP·C-C—
P>P°P±PsCћP°C,PsCћPSC- PrPsCfP»C-PrP¶PµPSPSC¶	PµC-PrPIP€C%PµPSPSC¶ CћC-PIPS¶ P°PjC-P»P°P·P€ PI PeCћPsPIC-; PiC-PrPIP€C%PµPSPSC¶ CћC-PIPS¶ P»C-PiP°P·P€; PiC-PiPsPeP°P»C-C”PjC-C¶; PiC-PiPsPSP°C,CћC-C”PjC-C¶, C%Ps PiPµCћPµPIP°P¶PSPs PiPsPiбћ™C¶P·P°PSP° P· PrC-P°CћPµC”Cћ C,P° P±P»CћPIP°PSPSC¶Pj; PrCfP¶Pµ CћC-PrPePs PSP°PrC...PsPrP€P»P€ PiPsPIC-PrPsPjP»PµPSPSC¶ PiCћPs PIP€PiP°PrPeP€ PiC-PrPIP€C%PµPSPSC¶ CfP€CћPsPIP°C,PePsPIP€C... CћC-PIPS-C-PI C,CћP°PSCfP°PjC-PSP°P· (PћPŸPŸ C- PћP·PŸ) Cf CћP°P·C- PIC-PrCfCfC,PSPsCfC,C- PiCћPsPiCћPµCfCfCћC†P€C... PjPµC,P°CfC,P°P·C-PI PiPµC†C-PSPeP€
P— P±PsPeCf Pjбћ™C¶P·PsPIPs- CfPePµP»PµC,PSPsC— CfP€CfC,PµPjP€ C,P° CfPiPsP»CfC†PSPsC— C,PeP°PSP€PSP€	PŸPePsCћPsC†PµPSPSC¶ Pjбћ™C¶P·C-PI P°P±Ps CfCfPrPsPjP€
P— P±PsPeCf PSP€CћPsPe C,P° CfPµC†PsPIP€PrC-P»CHPSPsC— CfP€CfC,PµPjP€	PµPsCћCfC€PµPSPSC¶ C,,CfPSPeC†C-C— PSP€CћPsPe C- PiPsCfC,CћP° PSP€CћPePsPIP° PSPµPrPsCfC,P°C,PSC-CfC,Ch P·P°P·PIP€C†P°PNё CfPiPsCfC,PµCћC-PiP°P»P€CfC¶ Cf PiP°C†C-C”PSC,C-PI P· C-PSC,,C-PeCfPIP°PSPSC¶Pj C,P°/P°P±Ps PiC-PiPsPIPsP»PµPjC-C”Cћ, C%Ps CћPsP·PIP€PSCfP»P°CfC¶ PIPSP°CfP»C-PrPsPe C,C¶P¶PePsC— C€P»CfPSPePsPIPs-PeP€C€PePsPIPsC— C,PsPeCfP€C†PSPsCfC,C-***; PSP€CћPePsPIP° PSPµPrPsCfC,P°C,PSC-CfC,Ch***
P— P±PsPeCf CfCfPrP€PS	P”C-PiPsC,PµPSP·C-C¶***
P— P±PsPeCf PiPµPiP°C,PsP±C-P»C-P°CћPSPsC— CfP€CfC,PµPjP€	PŸC,PµP°C,PsPiPµPiP°C,P€C,; CfC,PµP°C,PsP· PiPµC†C-PSPeP€

*PќP°PiCћP€PeP»P°Pr, PiPSPµPIPIPsC†P€CfC,PSP° PiPSPµPIPIPsPSC-C¶,
P±CћPsPSC...PsP»PµPiPµPSPµPIP€PNё P°CfPiPµCћPiC-P»CHPsP·, CfP€CfC,PµPjPSP€PNё
PeP°PSPrP€PrPsP·.

****P_hPiP_μCH₃C-P·C_rPIP°P»CH₃PSPëPN₂ PiP_μCH₃PiP_μCT_r, PiCH₃PëPi_r, CH₃P_μP°PeC,PëPIP°CT_rC-CT_r PiP_μPiP°C,PëC,C_r P', C_tPëC,PsPjP_μPiP°P»PsPIC-CH₃C_rCT_rPSPëPN₂ PePsP»C-C,,.**

*****P C-PrPeC-CT_rPSC- PIPëPiP°PrPePë PSPëCH₃PePsPIPsC— PSP_μPrPsCT_rC,P°C,PSPsCT_rC,C-, PiC-PiPsC,P_μPSP·C-C— P°P±Ps CT_rP_μCH₃C_tP_μPIPs-CT_rC_rPrPëPSPSPsC— PSP_μPrPsCT_rC,P°C,PSPsCT_rC,C- CT_rPiPsCT_rC,P_μCH₃C-PiP°P»PëCT_rCT_r C_r PiP°CT_rC-C”PSC,C-PI, CT_rPeC- PiP_μCH₃P_μPSP_μCT_rP»Pë P·PSP_μPIPsPrPSP_μPSPSCCT_r PIPSP°CT_rP»C-PrPsPe PrC-P°CH₃P_μC— C,P°/P°P±Ps P±P»CH₃PIP°PSPSCCT_r C_tPë CT_rP_μPiCT_rPëCT_rC_r.**

P_μPsPIC-PrPsPjP»P_μPSPSCCT_r PiCH₃Ps PiC-PrPsP·CH₃CH₃PIP°PSC- PiPsP±C-C_tPSC- CH₃P_μP°PeCT_rC-C—

P—PIC-C,C_rPIP°PSPSCCT_r PiCH₃Ps PiC-PrPsP·CH₃CH₃PIP°PSC- PiPsP±C-C_tPSC- CH₃P_μP°PeCT_rC-C— PiC-CT_rP»CT_r CH₃P_μC”CT_rC,CH₃P°CT_rC-C— P»C-PeP°CH₃CT_rCH₃PePsPiPs P·P°CT_rPsP±C_r C” PIP°P¶P»PëPIPëPj. P’PsPSPs PrP°C” P·PjPsPiC_r PiCH₃PsPrPsPIP¶CT_rPIP°C,Pë PjPsPSC-C,PsCH₃PëPSPi CT_rPiC-PIPIC-PrPSPsC€P_μPSPSCCT_r PePsCH₃PëCT_rC,CH₃/CH₃PëP·PëPe P»C-PeP°CH₃CT_rCH₃PePsPiPs P·P°CT_rPsP±C_r.

P₃P_μCH₃PjC-PS PiCH₃PëPrP°C,PSPsCT_rC,C-.

P—P°PiP_μC_tP°C,P°PSPëPN₂ C,,P»P°PePsPS: 4 CH₃PsPePë.

P_μC-CT_rP»CT_r CH₃PsP·P±P°PIP»P_μPSPSCCT_r: C...C-PjC-C_tPSP° C- C,,C-P·PëC_tPSP° CT_rC,P°P±C-P»CH₃PSC-CT_rC,CH₃ PiCH₃Pë P·P°CT_rC,PsCT_rC_rPIP°PSPSC- P±C_tP»P° PiCH₃PsPrP_μPjPsPSCCT_r,CH₃PsPIP°PSP° C_r CH₃PsP·C_tPëPSP°C... PrP»CT_r C-PSC,,C_rP·C-PN₂ (0,9 % CH₃PsP·C_tPëPS (PjP°CT_rP°/PsP±B₇TM C”Pj) PSP°C,CH₃C-CH C...P»PsCH₃PëPrC_r C,P° 5 % CH₃PsP·C_tPëPS (PjP°CT_rP°/PsP±B₇TM C”Pj) PiP»CH₃PePsP·Pë) PiCH₃Pë C,P_μPjPiP_μCH₃P°C,C_rCH₃C- 15B₇”25 B°C PiCH₃PsC,CT_rPiPsPj 12 PiPsPrPëPS P°P±Ps PiCH₃Pë C,P_μPjPiP_μCH₃P°C,C_rCH₃C- 2B₇”8 B°C PiCH₃PsC,CT_rPiPsPjB 48 PiPsPrPëPS, P·P° PSP°CT_rPIPSsCT_rC,C- P·P°C...PëCT_rC,C_r PIC-Pr CT_rPIC-C,P»P°.

P— PjC-PeCH₃PsP±C-PsP»PsPiC-C_tPSPsC— C,PsC_tPePë P·PsCH₃C_r CH₃PsP·C_tPëPS PiCH₃P_μPiP°CT_rP°C,C_r PiC-PrP»CT_rPiP°C” PSP_μPiP°PN₂PSPsPjC_r PIPëPePsCH₃PëCT_rC,P°PSPSC_h. PiPeC%₀Ps CH₃PsP·C_tPëPS PSP_μ PIPIP_μPrP_μPSPs PsPrCH₃P°P·C_r PiC-CT_rP»CT_r PiCH₃PëPiPsC,C_rPIP°PSPSCCT_r, C,Ps PIC-PrPiPsPIC-PrP°P»CH₃PSC-CT_rC,CH₃ P·P° C_rPjPsPIPë C,P° C,P_μCH₃PjC-PS P·P±P_μCH₃C-PiP°PSPSCCT_r CH₃PsP·C_tPëPSC_r PrPs PjPsPjP_μPSC,C_r PN₂PsPiPs PIPIP_μPrP_μPSPSCCT_r PSP_μCT_rP_μ PePsCH₃PëCT_rC,C_rPIP°C_t. PiPeC%₀Ps CH₃PsP·C_tPëPS PiPsC,C_rPIP°P»Pë PSP_μ PI PePsPSC,CH₃PsP»CH₃PsPIP°PSPëC... C,P° PIP°P»C-PrPsPIP°PSPëC... P°CT_rP_μPiC,PëC_tPSPëC... C_rPjPsPIP°C..., C,Ps PN₂PsPiPs CT_rP»C-Pr P·P±P_μCH₃C-PiP°C,Pë PiCH₃Pë 2B₇”8 B°C PiCH₃PsC,CT_rPiPsPj PSP_μ PrPsPIC€P_μ PSC-P¶ 24 PiPsPrPëPSPë.

PjPjPsPIPë P·P±P_μCH₃C-PiP°PSPSCCT_r.

P—P±P_μCH₃C-PiP°C,Pë PI PsCH₃PëPiC-PSP°P»CH₃PSC-PN₂ C_rPiP°PePsPIC_tC- PrP»CT_r P·P°C...PëCT_rC,C_r PIC-Pr CT_rPIC-C,P»P° PI PSP_μPrPsCT_rC,C_rPiPSPsPjC_r PrP»CT_r PrC-C,P_μPN₂ PjC-CT_rCT_rC- PiCH₃Pë C,P_μPjPiP_μCH₃P°C,C_rCH₃C- PSP_μ PIPëC%₀P_μ 25 B°P_Y. P_kP_μ

P·P°PjPsCḡPsP¶CřPI P°C,Pë.

PkPµCÍCžPjC-CÍPSC-CÍC,CH.

P°P°PSPëPNë P»C-PeP°CḡCÍCHPePëPNë P·P°CÍC-P± PSPµ CÍP»C-Pr P·PjC-CëCřPI P°C,Pë P·C-PSCëPëPjPë P»C-PeP°CḡCÍCHPePëPjPë P·P°CÍPsP±P°PjPë, PsPeCḡC-Pj PIPeP°P·P°PSPëC... CřCḡPsP·PrC-P»C- B«PhCÍPsP±P»PëPIC- P·P°C...PsPrPë P±PµP·PïPµPePëB».

PJPïP°PePsPIPeP°.

PµPs 2 PjP», 5 PjP» P°P±Ps 15 PjP» Cř C„P»P°PePsPSC-; PïPs 1 C„P»P°PePsPSCř PI PeP°CḡC,PsPSPSC-PNë PePsCḡPsP±C†C-.

PљP°C,PµPiPsCḡC-C¶ PIC-PrPïCřCÍPeCř.

P—P° CḡPµC†PµPïC,PsPj.

P°PëCḡPsP±PSPëPe.

PḡPeP°C-PrP° P°PjP±P¶/AqVida GmbH.

PњC-CÍC†PµP·PSP°C...PsPrP¶PµPSPSC¶ PIPëCḡPsP±PSPëPeP° C,P° P°PrCḡPµCÍP° PjC-CÍC†C¶ PïCḡPsPIP°PrP¶PµPSPSC¶ PNëPsPiPs PrC-C¶P»CHPSPsCÍC,C-.

PљP°PNëP·PµCḡ-P°C-P»CHPiPµP»CHPj-PëC,Cḡ. 89, 20355 P°P°PjP±CřCḡPi, PќC-PjPµC†C†PëPSP°/Kaiser-Wilhelm-Str. 89, 20355 Hamburg, Germany.

P—P°C¶PIPSPëPe.

PḡPjP°PeCÍP° P>C,Pr/Amaxa Ltd.

PњC-CÍC†PµP·PSP°C...PsPrP¶PµPSPSC¶ P·P°C¶PIPSPëPeP°.

31 P°P¶PsPS P†CÍP»C-Pï PŸC,CḡC-C,, P>PsPSPrPsPS SW1P 4FE, P°PµP»PëPeP° P°CḡPëC,P°PSC-C¶/31 John Islip Street, London SW1P 4FE, United Kingdom.