LISMEDFARM S.R.L.
Șos. Munceşti, 167/B, MD – 2002, mun. Chișinău, Republica Moldova
tel.: 022-80-47-98, 022-55-64-38, 022-56-94-91, e-mail: oficiu@lismedfarm.md,
web: https://lismedfarm.md, c/f: 1003600113573, TVA: 0304618, director – Ecaterina Chitic

Anexa nr. 7
la Documentația standard
Ordinul Ministrului Finanțelor
nr. 115 din 15 septembrie 2021

CERERE DE PARTICIPARE

Către CENTRUL PENTRU ACHIZITII PUBLICE CENTRALIZATE IN SANATATE, MD-2005,

Republica Moldova, mun. Chișinău, or. Chișinău, str. G. Vieru 22/2

Stimaţi domni,

Ca urmare a anunțului/invitației de participare/de preselecție apărut în Buletinul achizițiilor publice și/sau Jurnalul Oficial al Uniunii Europene, nr ocds-b3wdp1-MD-1732642177049 din 26.11.2024, privind aplicarea procedurii pentru atribuirea contractului Achiziţionarea medicamentelor pentru realizarea Programului Naţional de prevenire și control HIV/SIDA și ITS pentru anul 2025 (repetat nr. 1), noi, Lismedfarm S.R.L., am luat cunoștință de condițiile și de cerințele expuse în documentația de atribuire și exprimăm prin prezenta interesul de a participa, în calitate de ofertant/candidat, neavând obiecții la documentația de atribuire.

Data completării 11.12.2024

Digitally signed by Chitic Ecaterina
Date: 2024.12.12 08:59:45 EET
Reason: MoldSign Signature
Location: Moldova
MOLDOVA EUROPEANĂ

Cu stimă,

Ofertant/candidat

Vlad Chitic, director executiv

Lismedfarm S.R.L.

REPUBLICA MOLDOVA

CERTIFICAT DE ÎNREGISTRARE

SOCIETATEA CU RĂSPUNDERE LIMITATĂ "LISMEDFARM"
ESTE ÎNREGISTRATĂ LA CAMERA ÎNREGISTRĂRII DE STAT

Numărul de indentificare de stat - codul fiscal
1003600113573

Data înregistrării **07.12.2001**

Data eliberării **17.01.2005**

Bobeica Ion, registrator de stat
Funcția, numele, prenumele persoanei care a eliberat certificatul

semnătura

CAMERA ÎNREGISTRĂRII DE STAT 201

MD 0018019

L.Ș.

EXIMBANK

BANCA COMERCIALĂ "EXIMBANK" S.A.
SUCURSALA Nr.20
Nr. de ieşire 07/597

25. IUL. 2023

CERTIFICAT

Prin prezentul, B.C. "EXIMBANK" S.A., Sucursala nr.20, confirmă faptul deţinerii de către compania "LISMEDFARM" SRL, IDNO 1003600113573, a următoarelor conturi de decontare:

Valuta	Nr. Cont	Cod IBAN
MDL	222401475MDL	MD73EX0000000222401475MD
EUR	222451600EUR	MD13EX1900000222451600EU
USD	222451600USD	MD32EX1900000222451600US
RUB	225150633RUB	MD23EX1900000225150633RU

Certificatul este eliberat pentru a fi prezentat la cerere.

Coordonator Sucursala nr. 20
Postu Diana

BANCA COMERCIALĂ "EXIMBANK" S.A. SUCURSALA Nr.20 EXIMBANK 2 IDNO 1002600010273 REPUBLICA MOLDOVA, mun. CHIŞINĂU

Ex.: Belecci Lilia
Tel.: 022 301-304

GUVERNUL REPUBLICII MOLDOVA

SERVICIUL FISCAL DE STAT

MCabinet
PORTALUL GUVERNAMENTAL AL CETĂȚEANULUI ȘI AL UNITĂȚILOR DE DREPT

CERTIFICAT

privind lipsa sau existența restanțelor față de bugetul public național

Nr. № **1441573**

Din От **11.12.2024 14:41**

DATE DESPRE CONTRIBUABIL / ИНФОРМАЦИЯ О НАЛОГОПЛАТЕЛЬЩИКЕ

Codul fiscal / Numărul de identificare
Фискальный код / Идентификационный номер

1003600113573

Denumirea
Наименование

Societatea cu Răspundere Limitată LISMEDFARM

ATESTAREA LIPSEI SAU EXISTENȚEI RESTANȚELOR CONFORM DATELOR SISTEMULUI INFORMAȚIONAL AUTOMATIZAT / ПОДТВЕРЖДЕНИЕ ОТСУТСВИЯ ИЛИ НАЛИЧИЯ ЗАДОЛЖНОСТЕЙ СОГЛАСНО ДАННЫМ ИНФОРМАЦИОННОЙ АВТОМАТИЗИРОВАННОЙ СИСТЕМЫ

La data emiterii prezentului certificat restanța față de bugetul public național constituie
На дату выдачи данной справки задолжность перед национальном публичным бюджетом составляет

0 MDL

VALABIL PÂNĂ LA / ДЕЙСТВИТЕЛЕН ДО **26.12.2024 14:41**

Prezentul document este eliberat în temeiul Art. 29, alin. (3) din Legea cu privire la registre nr. 71/2007 și în baza datelor furnizate de Serviciul Fiscal de Stat în Portalul Guvernamental al Cetățeanului și al Unităților de Drept / Справка выдана в соответсвие со ст. 29 п. (3) Закона о реестрах № 71/2007 на основании данных, предостоставленных Государственной налоговой службой на Портале Правительства Гражданина и Юридических Лиц.

Generat și semnat de Portalul Guvernamental al Cetățeanului și al Unităților de Drept la **11.12.2024 14:41**

Prezentul certificat este semnat electronic în conformitate cu Legea nr.124 din 19.05.2022
Сертификат подписан электронной попдписью в соответсвие с Законом № 124 от 19.05.2022

Certificatul este descărcat din Portalul Guvernamental al Cetățeanului și al Unităților de Drept (mcabinet.gov.md) și este semnat electronic de către posesorul acestui portal și are aceiași valoare juridică ca și documentele eliberate pe suport de hârtie de către organele cu atribuții de administrare fiscală. Verificarea autenticității semnăturii electronice poate fi realizată cu ajutorul Serviciului Guvernamental de Semnătură Electronică (msign.gov.md)

Сертификат скачен с Правительственного Портала Гражданина и Юридических Лиц (mcabinet.gov.md) и подписан электронной подписью владельца портала и имеет такаю же юридическую силу, как и документы выдаваемые на бумаге органами налоговой администрации. Проверку подлиности электронной подписи можно осуществить с помощью Государсвенной Службой Электронной Подписью (msign.gov.md)

LISMEDFARM S.R.L.
Șos. Munceşti, 167/B, MD – 2002, mun. Chișinău, Republica Moldova
tel.: 022-80-47-98, 022-55-64-38, 022-56-94-91, e-mail: oficiu@lismedfarm.md,
web: https://lismedfarm.md, c/f: 1003600113573, TVA: 0304618, director – Ecaterina Chitic

Anexa nr. 8
la Documentația standard
Ordinul Ministrului Finanțelor
nr. 115 din 15 septembrie 2021

DECLARAŢIE
PRIVIND VALABILITATEA OFERTEI

Către CENTRUL PENTRU ACHIZITII PUBLICE CENTRALIZATE IN SANATATE, MD-2005,

Republica Moldova, mun. Chișinău, or. Chișinău, str. G. Vieru 22/2

Stimaţi domni,

Ne angajăm să menținem oferta valabilă, **privind** Achiziționarea medicamentelor pentru realizarea Programului Național de prevenire și control HIV/SIDA și ITS pentru anul 2025 (repetat nr. 1) (se indică obiectul achiziției) **prin procedura de achiziție** Licitație deschisă (tipul procedurii de achiziție)**,** pentru o durată de 90 (nouăzeci) zile, (durata în litere și cifre), respectiv până la data de 18.03.2025 (ziua/luna/anul), și ea va rămâne obligatorie pentru noi și poate fi acceptată oricând înainte de expirarea perioadei de valabilitate.

Data completării 11.12.2024

Cu stimă,
Ofertant/candidat
Vlad Chitic, director executiv
Lismedfarm S.R.L.

LISMEDFARM S.R.L.
Șos. Munceşti, 167/B, MD – 2002, mun. Chișinău, Republica Moldova
tel.: 022-80-47-98, 022-55-64-38, 022-56-94-91, e-mail: oficiu@lismedfarm.md,
web: https://lismedfarm.md, c/f: 1003600113573, TVA: 0304618, director – Ecaterina Chitic

CENTRUL PENTRU ACHIZITII PUBLICE CENTRALIZATE IN SANATATE

Declarație

Declarăm următoarele pentru LPnr. ocds-b3wdp1-MD-1732642177049 din 12.12.2024:

Termenul de valabilitate restant (la momentul livrării) al medicamentelor va fi nu mai mic de 80 % pentru produse cu un termen total de valabilitate de pînă la 2 ani, și nu mai mic de 60 % pentru produse cu un termen total de valabilitate mai mare de 2 ani.

Cu respect,

Director executiv Lismedfarm S.R.L. Vlad Chitic

Contact: vlad.chitic@lismedfarm.md, +37379981005

APROBAT
prin Ordinul
Ministrului Finanțelor
nr. 146 din 24.11.2020

FORMULARUL STANDARD AL DOCUMENTULUI UNIC DE ACHIZIȚII EUROPEAN

1. Documentul unic de achiziții european, (în continuare, DUAE) este o declarație pe proprie răspundere, prin care operatorul economic confirmă îndeplinirea criteriilor de calificare și selecție necesare în cadrul procedurilor de achiziție publică în Republica Moldova.
2. Formularul este completat, semnat electronic și transmis autorității contractante la depunerea ofertei.
3. Un DUAE depus de către operatorul economic în cadrul unei proceduri de achiziție publică anterioară poate fi reutilizat, cu condiția ca informațiile cuprinse în formular să fie corecte și valabile la data depunerii acestuia.
4. Ofertantul care prezintă în DUAE informații false sau documentele justificative prezentate nu confirmă informația indicată în documentul prezentat este exclus din procedura de achiziție publică și/sau poate răspunde conform legislației.
5. Formularul DUAE este constituit din 7 capitole, și anume:

1) Capitolul I. Informații privind procedura de achiziție publică și autoritatea/entitatea contractantă;
2) Capitolul II. Informații referitoare la operatorul economic;
3) Capitolul III. Motive de excludere din cadrul procedurii de achiziție publică;
4) Capitolul IV. Criteriile de calificare și selecție a operatorilor economici;
5) Capitolul V. Indicații generale pentru criteriile de selecție a operatorilor economici;
6) Capitolul VI. Preselecția candidaților pentru procedura de atribuire a contractului de achiziție publică;
7) Capitolul VII. Declarații finale.

6. Prezentarea formularului DUAE la depunerea ofertei care nu este conform cu cerințele stabilite în Documentația de atribuire duce la respingerea ofertei.

Capitolul I. Informații privind procedura de achiziție publică și autoritatea/entitatea contractantă

Compartimentul se completează doar de către autoritatea/entitatea contractantă.

Cod poziție	Conținutul cerinței	Răspuns
1	2	3
A. Informații despre publicare		
1A.1	Numărul anunțului/invitației publicate în Buletinul achizițiilor publice, și după caz numărul anunțului publicat în Jurnalul Oficial al Uniunii Europene	ocds-b3wdp1-MD-1732642177049
B. Identitatea autorității/entității contractante		
1B.1	Denumirea autorității/entității contractante	**CENTRUL PENTRU ACHIZITII PUBLICE CENTRALIZATE IN SANATATE**
1B.2	Număr unic de identificare (IDNO) a autorității/entității contractante	**1016601000212**

Capitolul II. Informații referitoare la operatorul economic

Compartimentul se completează doar de către operatorii economici.

Cod	Conținutul cerințelor	Răspuns

poziție		
1	2	3
A. Informații privind operatorul economic		
2A.1	Denumirea operatorul economic	Lismedfarm S.R.L.
2A.2	Țara	Republica Moldova
2A.3	Cod poștal	MD-2002
2A.4	Oraș/Localitate	Mun. Chisinau
2A.5	Adresa juridică	sos. Muncesti 167/B
2A.6	Pagina web	Lismedfarm.md
2A.7	Persoana sau persoanele de contact	Vlad Chitic
2A.7.1	*Telefon*	*+37379981005*
2A.7.2	*Adresa de e-mail*	*vlad.chitic@ lismedfarm.md*
2A.8	Număr unic de identificare (IDNO/IDNP)	1003600113573
2A.9	Numărul cod TVA	0304618
2A.10	Forma organizatorico-juridică a activității de antreprenoriat	Societate cu Răspundere Limitată
2A.11	Informația cu privire la numele acționarilor / asociaților / beneficiarului efectiv	
2A.11.1	Numele acționarilor / asociaților	100 % - Chitic Ecaterina
2A.11.2	Numele beneficiarului efectiv *[**beneficiar efectiv** – persoană fizică ce deține sau controlează în ultimă instanță o persoană fizică sau juridică ori beneficiar al unei societăți de investiții sau administrator al societății de investiții, ori persoană în al cărei nume se desfășoară o activitate sau se realizează o tranzacție și/sau care deține, direct sau indirect, dreptul de proprietate sau controlul asupra a cel puțin 25% din acțiuni sau din dreptul de vot al persoanei juridice ori asupra bunurilor aflate în administrare fiduciară]*	100% - Chitic Ecaterina
2A.11.3	*Cetățenia beneficiarului efectiv (legătură juridico-politică permanentă a persoanei fizice definite conform poziției 2A.11.2)*	Chitic Ecaterina – Republica Moldova (MD) și România (RO)
2A.12	Operatorul economic este: • întreprindere mică • întreprindere mijlocie • și altele	Întreprindere mică
2A.13	În cazul în care achiziția este rezervată: operatorul economic este un atelier protejat sau o întreprindere socială, sau va asigura executarea contractului în contextul programelor de angajare protejată?	Da ☒ Nu
2A.13.1	*Dacă da, care este procentul corespunzător de lucrători cu dizabilități sau defavorizați?*	*0*
2A.13.2	*Specificați cărei sau căror categorii de lucrători cu dizabilități sau defavorizați le aparțin angajații în cauză?*	*0*
2A.14	Operatorul economic participă la procedura de achiziții publice împreună cu alți operatori economici?	Da ☒ Nu
2A.14.1	*Dacă Da, precizați rolul operatorului economic în cadrul grupului (lider, responsabil cu îndeplinirea unor sarcini specifice, etc).*	|*text*|
2A.14.2	*Numiți operatorii economici care participă la procedura respectivă de achiziție publică.*	|*text*|
2A.14.3	*Specificați denumirea grupului participant.*	|*text*|

Notă. Dacă ați răspuns Da la întrebarea 2A.14, asigurați-vă ca operatorii economici menționați să prezinte un formular DUAE separat.		
B. Informații privind reprezentanții operatorului economic		
Indicați numele persoanei (persoanelor) împuternicită (împuternicite) să îl reprezinte pe operatorul economic în scopurile prezentei proceduri de achiziție publică.		
2B.1	Nume și prenume	Vlad Chitic
2B.2	Poziție/acționând în calitate de	Director executiv
2B.3	Țară	Republica Moldova
2B.4	Telefon	079981005
2B.5	Adresa de e-mail	vlad.chitic@ lismedfarm.md
C. Informații privind utilizarea capacităților altor entități		
2C.1	Operatorul economic utilizează capacitățile altor entități pentru a satisface criteriile de selecție prevăzute în capitolul IV, precum și (dacă este cazul) criteriile și regulile menționate în capitolul V de mai jos?	Da ☒ Nu
Notă. Dacă ați răspuns Da la întrebarea 2C.1, prezentați un formular DUAE separat care să cuprindă informațiile solicitate în secțiunile A și B din capitolul respectiv și din capitolul III pentru fiecare dintre entitățile în cauză, completat și semnat în mod corespunzător de entitățile în cauză. Atragem atenția asupra faptului că trebuie incluși, de asemenea, tehnicienii sau organismele tehnice implicate, indiferent dacă fac sau nu parte din întreprinderea operatorului economic, în special cei care răspund de controlul calității și, în cazul contractelor de achiziții publice de lucrări, tehnicienii sau organismele tehnice la care poate face apel operatorul economic în vederea executării lucrărilor. În măsura în care este relevant pentru capacitatea (capacitățile) specifică (specifice) utilizată (utilizate) de operatorul economic, includeți informațiile prevăzute în capitolele IV și V pentru fiecare dintre entitățile în cauză.		
D. Informații privind subcontractanții pe ale căror capacități operatorul economic se bazează		
2D.1	Operatorul economic intenționează să subcontracteze vreo parte din contract cu alți operatori economici?	Da ☒ Nu
2D.1.1	*Dacă Da, enumerați subcontractanții propuși.*	|*text*|

Capitolul III. Motive de excludere din cadrul procedurii de achiziție publică

Compartimentul se completează de către operatorii economici.

Cod poziție	Conținutul cerințelor	Răspuns
A. Motive referitoare la condamnări prin hotărârea definitivă a unei instanțe judecătorești		
1	**2**	**3**
3A.1	**Participare la o organizație criminală.** Operatorul economic însuși sau orice persoană care este membru al organismului de administrare, de conducere sau de supraveghere al acestuia sau care are putere de reprezentare, de decizie sau de control în cadrul acestuia a făcut obiectul unei condamnări pronunțate printr-o hotărâre definitivă pentru participare la o organizație criminală, printr-o condamnare pronunțată cu cel mult cinci ani în urmă sau în care continuă să se aplice o perioadă de excludere prevăzută în mod direct în condamnare?	Da ☒ Nu
3A.2	**Corupție.** Operatorul economic însuși sau orice persoană care este membru al organismului de administrare, de conducere sau de supraveghere al acestuia sau care are putere de reprezentare, de decizie sau de control în cadrul acestuia a făcut obiectul unei condamnări pentru corupție pronunțate printr-o hotărâre definitivă, printr-o condamnare pronunțată cu cel mult cinci ani în	Da ☒ Nu

	urmă sau în care continuă să se aplice o perioadă de excludere prevăzută în mod direct în condamnare?	
3A.3	**Fraude.** Operatorul economic însuși sau orice persoană care este membru al organismului de administrare, de conducere sau de supraveghere al acestuia sau care are putere de reprezentare, de decizie sau de control în cadrul acestuia a făcut obiectul unei condamnări pentru fraudă pronunțate printr-o hotărâre definitivă, printr-o condamnare pronunțată cu cel mult cinci ani în urmă sau în care continuă să se aplice o perioadă de excludere prevăzută în mod direct în condamnare?	Da ☒ Nu
3A.4	**Infracțiuni teroriste sau infracțiuni legate de activitățile teroriste.** Operatorul economic însuși sau orice persoană care este membru al organismului de administrare, de conducere sau de supraveghere al acestuia sau care are putere de reprezentare, de decizie sau de control în cadrul acestuia a făcut obiectul unei condamnări pentru infracțiuni teroriste sau infracțiuni legate de activități teroriste, pronunțate printr-o hotărâre definitivă, printr-o condamnare pronunțată cu cel mult cinci ani în urmă sau în care continuă să se aplice o perioadă de excludere prevăzută în mod direct în condamnare?	Da ☒ Nu
3A.5	**Spălare de bani sau finanțarea terorismului.** Operatorul economic însuși sau orice persoană care este membru al organismului de administrare, de conducere sau de supraveghere al acestuia sau care are putere de reprezentare, de decizie sau de control în cadrul acestuia a făcut obiectul unei condamnări pentru infracțiuni teroriste sau infracțiuni legate de activități teroriste, pronunțate printr-o hotărâre definitivă, printr-o condamnare pronunțată cu cel mult cinci ani în urmă sau în care continuă să se aplice o perioadă de excludere prevăzută în mod direct în condamnare?	Da ☒ Nu
3A.6	**Exploatarea prin muncă a copiilor și alte forme de trafic de persoane.** Operatorul economic însuși sau orice persoană care este membru al organismului de administrare, de conducere sau de supraveghere al acestuia sau care are putere de reprezentare, de decizie sau de control în cadrul acestuia a făcut obiectul unei condamnări pronunțate printr-o hotărâre definitivă pentru exploatare prin muncă a copiilor și alte forme de trafic de persoane, printr-o condamnare pronunțată cu cel mult cinci ani în urmă sau în care continuă să se aplice o perioadă de excludere prevăzută în mod direct în condamnare?	Da ☒ Nu
3A.7	În cazul că răspunsul este Da pentru cel puțin una din întrebările 3A.1 – 3A.6, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?	Da Nu
3A.7.1	*Dacă Da, descrieți aceste măsuri.*	*|text|*
B. Motive privind plata impozitelor sau/și a contribuțiilor de asigurări sociale		
	Plata impozitelor	
3B.1	Operatorul economic și-a onorat obligațiile cu privire la plata impozitelor, taxelor și contribuțiilor sociale în conformitate cu prevederile legale în vigoare în Republica Moldova sau în țara în care este stabilit?	☒ Da Nu

3B.1.1	*Dacă Nu, în ce mod a fost stabilită obligația cu privire la plata impozitelor, taxelor și contribuțiilor sociale?*	*|text|*
3B.1.2	*În cazul în care, încălcarea cu referire la obligațiile privind plata impozitelor, taxelor și contribuțiilor sociale a fost stabilită printr-o hotărâre judecătorească sau administrativă, această decizie este definitivă?*	Da Nu
3B.1.3	*În cazul în care, încălcarea cu referire la obligațiile privind plata impozitelor, taxelor și contribuțiilor sociale a fost stabilită printr-o hotărâre judecătorească sau administrativă, precizați data și numărul deciziei.*	*|text|*
3B.2	Operatorul economic beneficiază, în condițiile legii, de eșalonarea obligațiilor de plată a impozitelor, taxelor și contribuțiilor de asigurări sociale ori de alte facilități în vederea plății acestora, inclusiv a majorărilor de întârziere (penalităților) și/sau a amenzilor? Notă: *Se completează doar în cazul în care ați răspuns Nu, la întrebarea din 3B.1.*	Da Nu
3B.2.1	*Dacă Da, operatorul economic este în măsură să furnizeze actul privind eșalonarea obligațiilor de plată a impozitelor, taxelor și contribuțiilor de asigurări sociale ori de alte facilități în vederea plății acestora?*	Da Nu
3B.3	Operatorul economic este în măsură să furnizeze un certificat cu privire la plata impozitelor sau să furnizeze informații privind onorarea obligațiilor fiscale?	☒ Da Nu
3B.4	Informațiile privind lipsa/existența restanțelor față de bugetul public național sunt disponibile gratuit pentru autorități, prin accesarea unei baze de date naționale? Dacă da, specificați informația care ar permite verificarea.	Adresa de internet: https://date.gov.md/open/company-details Autoritatea sau organismul emitent(ă): Serviciul Fiscal de Stat al Republicii Moldova Referința exactă a documentației: Cautare prin codul fiscal
C. Includerea în lista de interdicție a operatorilor economici		
3C.1	Operatorul economic este înscris în lista de interdicție a operatorilor economici?	Da ☒ Nu
3C.1.1	*În cazul că răspunsul este Da pentru întrebarea 3C.1, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	Da Nu
3C.1.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
D. Motive legate de insolvabilitate, conflicte de interese sau abateri profesionale		
	Obligațiile aplicabile în domeniul mediului, muncii și asigurărilor sociale	
3D.1	Operatorul economic a încălcat obligațiile în domeniul mediului în ultimii 3 ani?	Da ☒ Nu
3D.1.1	*În cazul că răspunsul este Da pentru întrebarea 3D.1, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a*	Da Nu

	demonstra fiabilitatea, în pofida existenței unui motiv de excludere?	
3D.1.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
3D.2	Operatorul economic a încălcat obligațiile în domeniul social în ultimii 3 ani?	Da ☒ Nu
3D.2.1	*În cazul că răspunsul este Da pentru întrebarea 3D.2, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	Da Nu
3D.2.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
3D.3	Operatorul economic a încălcat obligațiile în domeniul muncii în ultimii 3 ani?	Da ☒ Nu
3D.3.1	*În cazul că răspunsul este Da pentru întrebarea 3D.3, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	Da Nu
3D.3.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
	Insolvabilitatea	
3D.4	Operatorul economic este în situație de insolvabilitate sau de lichidare a activității antreprenoriale ca urmare a unei hotărârii judecătorești?	Da ☒ Nu
3D.4.1	*În cazul că răspunsul este Da pentru întrebarea 3D.4, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	Da Nu
3D.4.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
	Active administrate de lichidator	
3D.5	Activele operatorului economic sunt administrate de un lichidator sau de o instanță?	Da ☒ Nu
3D.5.1	*În cazul că răspunsul este Da pentru întrebarea 3D.5, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	Da Nu
3D.5.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
	Activitățile economice sunt suspendate	
3D.6	Activitățile economice ale operatorului economic sunt suspendate?	Da ☒ Nu
3D.6.1	*În cazul că răspunsul este Da pentru întrebarea 3D.6, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	Da Nu
3D.6.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
	Acorduri cu alți operatori economici care vizează denaturarea concurenței	
3D.7	Operatorul economic, în ultimii 3 ani, a încheiat acorduri cu alți operatori economici care au ca obiect denaturarea concurenței, fapt constatat prin decizie a organului abilitat în acest sens?	Da ☒ Nu
3D.7.1	*În cazul că răspunsul este Da pentru întrebarea 3D.7, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	*Da Nu*
3D.7.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
	Conflict de interese	
3D.8	Operatorul economic se află într-o situație de conflict de interese care nu poate fi remediată?	Da ☒ Nu
3D.8.1	*În cazul că răspunsul este Da pentru întrebarea 3D.8, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	*Da Nu*
3D.8.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
	Etica profesională	
3D.9	Operatorul economic a fost condamnat, în ultimii 3 ani, prin hotărâre definitivă a unei instanțe judecătorești, pentru o faptă care	Da ☒ Nu

	a adus atingere eticii profesionale sau pentru comiterea unei greșeli în materie profesională?	
3D.9.1	*În cazul că răspunsul este Da pentru întrebarea 3D.9, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	Da Nu
3D.9.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*
	Integritatea	
3D.10	Operatorul economic, în ultimii 3 ani, se face vinovat de o abatere profesională, care îi pune la îndoială integritatea?	Da ☒ Nu
3D.10.1	*În cazul că răspunsul este Da pentru întrebarea 3D.10, puteți furniza dovezi care să arate că măsurile luate sunt suficiente pentru a demonstra fiabilitatea, în pofida existenței unui motiv de excludere?*	*Da Nu*
3D.10.2	*Dacă Da, descrieți aceste măsuri.*	*|text|*

Capitolul IV. Criteriile de calificare și selecție a operatorilor economici

Compartimentul se completează de către autoritatea/entitatea (coloana nr.2) contractantă și operatorii economici (coloana nr.3).

Cod poziție	**Conținutul cerințelor**	**Răspuns**
1	**2**	**3**
A. Capacitatea de exercitare a activității profesionale		
4A.1	Operatorul economic este în măsură să furnizeze documentul/documentele prin care se va demonstra înregistrarea acestuia?	☒ Da Nu
4A.1.1	*Dacă Da, indicați actele de înregistrare a activității antreprenoriale și genul (genurile) de activitate determinate de legislație, aferent obiectului procedurii de atribuire a contractului, în baza căreia întreprinderea are dreptul să execute viitorul contract de achiziție publică.*	*Licenta seria A MMI Nr. 002359 din 19.02.2024 – activitatea farmaceutica; Certificat de bunele practici de distribuție a medicamentelor de uz uman nr. AMDM.MD.GDP.H. 002.2023 din 10.05.2023; Extras din Registrul de stat al Persoanelor Juridice nr. 119749 din 02.11.2023:* *1. Comertul cu ridicarea produselor farmaceutice* *2. Comercul cu amanantul al produselor farmaceutice si de parfume* *3. Comertul cu*

		ridicarea al parfumelor si produselor cosmetice *4. Fabricarea produselor farmaceutice de baza* *5. Fabricarea preparatelor farmaceutice* *6. Importul, fabricarea, comercializarea, asistenta tehnica si (sau) reparatia dispozitivelor medicale si (sau) a opticii* *7. Comercul cu ridicarea al produselor alimentare, bauturilor si produselor din tutun* *8. Comertul cu amanuntul neefectuat prin magazine* *9. Intermedieri pentru vinzarea unui asortiment larg de parfumuri* *10. Comertul cu ridicarea al marfurilor nealimentare de larg consum* *11. Activitatea de cercetatea a pietei si de sondaj al opiniei publice* *12. Publicitatea* Notificarea privind initiarea activitatii de comert nr. 47299 din 30.05.2018 pentru depozit farmaceutic
4A.1.2	*Actele de înregistrare a activității antreprenoriale, sunt disponibile gratuit pentru autorități dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea.*	*Adresa de internet:* https://dataset.gov.md/ro/dataset/11736-date-din-registrul-de-stat-al-unitatilor-de-drept-privind-

		intreprinderile-inregistrate-in-repu
		Autoritatea sau organismul emitent(ă): *Agenția De Guvernare Electronică*
		Referința exactă a documentației: https://dataset.gov.md/dataset/a1f38191-f35c-4180-8d80-297851a08f60/resource/a523235f-11c9-44e9-af9b-3cd4ca0c3189/download/company-2024.05.20.xlsx
4A.2	Activitatea antreprenorială deține o certificare și/sau o autorizare echivalentă aferent obiectului procedurii de atribuire a contractului, în cadrul unui sistem național?	☒ Da Nu
4A.2.1	*Dacă Da, operatorul economic este în măsură să furnizeze documentul/documentele prin care se va demonstra certificarea și/sau autorizarea activității acestuia?*	☒ Da Nu
4A.2.3	*Actele privind certificarea sau autorizarea sunt disponibile gratuit pentru autorități, dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea.*	*Adresa de internet:* https://dataset.gov.md/ro/dataset/11736-date-din-registrul-de-stat-al-unitatilor-de-drept-privind-intreprinderile-inregistrate-in-repu
		Autoritatea sau organismul emitent(ă): *Agenția De Guvernare Electronică*
		Referința exactă a documentației: https://dataset.gov.md/dataset/a1f38191-f35c-4180-8d80-297851a08f60/resource/a523235f-11c9-44e9-af9b-3cd4ca0c3189/download/company-2024.05.20.xlsx
4A.3	Genurile de activitate, și/sau certificarea, și/sau autorizarea privind activitatea de întreprinzător, acoperă criteriile de selecție impuse de autoritatea/entitatea contractantă în anunțul/invitația de participare?	☒ Da Nu

B. Capacitatea economică și financiară		
	Declarații bancare	
4B.1	Operatorul economic este în măsură să furnizeze declarații bancare sau, după caz, dovezi privind asigurarea riscului profesional în conformitate cu cerințele din documentația de atribuire?	☒ Da Nu
4B.1.1	*Informația menționată la punctul 4B.1 este disponibilă gratuit pentru autorități, dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea ei.*	*Adresa de internet: |text|* *Autoritatea sau organismul emitent(ă): |text|* *Referința exactă a documentației: |text|*
	Cifra de afaceri anuală (volumul vânzărilor)	
4B.2	Operatorul economic este în măsură să demonstreze o cifră de afaceri anuală, după cum urmează: Valoare ___-__ Perioada ___-____ *Notă. Se completează de către autoritatea contractantă valoarea și perioada*	☒ Da Nu
4B.2.1	*Specificați care este cifra de afaceri anuală, conform datelor din raportul financiar.*	*94,511,274MDL* *2023*
	Cifra de afaceri medie anuală	
4B.3	Operatorul economic este în măsură să demonstreze o cifră medie anuală de afaceri, după cum urmează: Valoare ___-__ Perioada ___-____ *Notă. Se completează de către autoritatea contractantă valoarea și perioada*	☒ Da Nu
4B.3.1	*Specificați cifra de afaceri, conform datelor din raportul financiar.*	*2021* *84,401,052MDL* *2022* *95,300,233MDL* *2023* *94,511,274MDL*
	Raport financiar	
4B.4	Operatorul economic este în măsură să furnizeze raportul financiar înregistrat, extrase din raportul financiar?	☒ Da Nu
4B.5	Informațiile privind situația economică și financiară sunt disponibile gratuit pentru autorități, dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea.	Adresa de internet: Sfs.md Autoritatea sau organismul emitent(ă): Serviciul Fiscal de Stat al Republicii Moldova Referința exactă a documentației: |text|
C. Capacitatea tehnică și/sau profesională		
	Operatorul economic este în măsură să furnizeze documentele	☒ Da Nu

4C.1	solicitate de către autoritatea/entitatea contractantă în anunțul de participare, care demonstrează capacitatea tehnică și/sau profesională pentru executarea viitorului contract.	
4C.1.1	*Informațiile privind capacitatea tehnică și/sau profesională sunt disponibile gratuit pentru autorități, dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea*.	*Adresa de internet: tender.gov.md/ro/contracte-atribuite* *Autoritatea sau organismul emitent(ă): Agenția Achiziții Publice* *Referința exactă a documentației: Informatie poate fi găsită folosind numele companiei*
	Instalații tehnice și măsuri de asigurare a calității	
4C.2	Operatorul economic este în măsură să furnizeze detalii referitoare la tehnicieni sau organismele tehnice, specificate în anunțul de participare/documentația de atribuire, pe care autoritatea/entitatea contractantă le poate solicita, în special cele responsabile de controlul calității în legătură cu acest exercițiu de achiziție publică?	☒ Da Nu
4C.3	Operatorul economic este în măsură să furnizeze o informație cu privire la sistemele de management și de trasabilitate utilizate în cadrul lanțului de aprovizionare?	☒ Da Nu
4C.3.1	*Informațiile sunt disponibile gratuit pentru autorități, dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea*.	*Adresa de internet: |text|* *Autoritatea sau organismul emitent(ă): |text|* *Referința exactă a documentației: |text|*
	Utilaje, instalații și echipament tehnic	
4C.4	Operatorul economic dispune de utilaje și echipament necesar pentru îndeplinirea corespunzătoare a contractului de achiziție publică?	☒ Da Nu
4C.5	Operatorul economic este în măsură să furnizeze o informație cu privire la dotările specifice, utilajul și echipamentul necesar pentru îndeplinirea contractului, conform cerințelor stabilite în anunțul de participare și documentația de atribuire?	☒ Da Nu
	Pregătirea profesională și calificarea personalului	
4C.6	Operatorul economic are în cadrul întreprinderii personal calificat conform cerințelor stabilite în anunțul de participare sau în documentația de atribuire?	☒ Da Nu
4C.7	Operatorul economic este în măsură să furnizeze o informație privind personalul de specialitate propus pentru executarea contractului, conform cerințelor stabilite în anunțul de participare și documentația de atribuire?	☒ Da Nu
4C.8	Indicați efectivele medii anuale de personal angajat din ultimii trei ani de activitate.	2021 24 2022 21 2023 23
	Numărul membrilor personalului de conducere	

4C.9	Indicați numărul membrilor personalului de conducere ale operatorului economic pe parcursul ultimilor trei ani.	2021 5 2022 2 2023 2
	Mostre, descrieri, fotografii	
4C.10	Operatorul economic este în măsură să furnizeze eșantioane (mostre), descrieri și/sau fotografii ale produselor/serviciilor care urmează să fie furnizate/prestate, conform cerințelor stabilite în documentația de atribuire?	☒ Da Nu
	Pentru contractele de achiziție publică de lucrări	
4C.11	În perioada de referință, operatorul economic a îndeplinit lucrări specifice sau similare obiectului de achiziție indicat în anunțul de participare și în documentația de atribuire?	Da ☒ Nu
4C.11.1	*Dacă Da, enumerați-le specificând descrierea lucrărilor, valoarea lor, data de începere, data procesului verbal de recepție la terminarea lucrărilor, beneficiarul și altă informație relevantă.*	|*text*|
	Pentru contractele de achiziție publică de bunuri	
4C.12	În perioada de referință, operatorul economic a efectuat livrări specifice obiectului de achiziție indicat în anunțul de participare și în documentația de atribuire?	☒ Da Nu
4C.12.1	*Dacă Da, enumerați-le specificând descrierea livrărilor, valoarea lor, data de începere, data furnizării, beneficiarul și altă informație relevantă.*	*Achiziționarea centralizată de consumabile de laborator conform necesităților IMSP, pentru anul 2020 - 611.701,95 - 21.04.2020 – Mai multe IMSP-uri* *Achiziționarea echipamentelor de protecție în scopul diminuării consecințelor negative ale COVID-19 pentru anul 2020 (repetat) - 36.028.000,00 - 27.03.2020 - Centrul pentru achizitii publice centralizate in sanatate* *Articole Parafarmaceutice si Consumabile pentru anul 2020 - 14.500,00 - 02.06.2020 - IMSP Spitalul de Traumatologie si Ortopedie*

		Articole parafarmaceutice pentru anul 2020 conform necesităților IMSP SCM 1 - 10.504,70 - 10.03.2020 - IMSP Spitalul Clinic Municipal nr 1
	Pentru contractele de achiziție publică de servicii	
4C.13	În perioada de referință, operatorul economic a prestat servicii similare cu obiectul de achiziție indicat în anunțul de participare și în documentația de atribuire?	Da ☒ Nu
4C.13.1	*Dacă Da, enumerați-le specificând descrierea serviciilor, valoarea lor, durata de execuție, data începerii, beneficiarul și altă informație relevantă.*	|*text*|
4C.14	În cazul că răspunsul este Da pentru una din întrebările 4C.11 – 4C.13, puteți furniza dovezi prin care se va demonstra îndeplinirea lucrărilor, livrarea bunurilor, prestarea serviciilor similare conform cerințelor documentației de atribuire?	Da Nu
D. Standarde de asigurare a calității		
4D.1	Operatorul economic este în măsură să furnizeze certificate emise de organisme independente prin care se atestă faptul că operatorul economic respectă standardele de asigurare a calității conform cerințelor stabilite în anunțul de participare și în documentația atribuire?	☒ Da Nu
4D.2	Informațiile privind standardele de asigurare a calității, sunt disponibile gratuit pentru autorități, dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea.	Adresa de internet: |text|
		Autoritatea sau organismul emitent(ă): |text|
		Referința exactă a documentației: |text|
E. Standarde de protecție a mediului		
4E.1	Operatorul economic este în măsură să furnizeze certificate emise de organisme independente prin care se atestă faptul că operatorul economic respectă standardele de protecție a mediului, conform cerințelor stabilite în anunțul de participare și în documentația de atribuire?	Da ☒ Nu
4E.2	Informațiile privind standardele de protecția mediului, sunt disponibile gratuit pentru autorități, dintr-o bază de date națională? Dacă da, specificați informația care ar permite verificarea.	Adresa de internet: |text|
		Autoritatea sau organismul emitent(ă): |text|
		Referința exactă a documentației: |text|
F. Permiterea controalelor		
4F.1	Operatorul economic permite efectuarea verificărilor de către autoritatea/entitatea contractantă referitor la capacitățile economice și financiare, de producție sau tehnice privind executarea viitorului	☒ Da Nu

	contract de achiziție publică?	

Capitolul V. Indicații generale pentru criteriile de calificare și selecție

Compartimentul se completează de către autoritatea/entitatea contractantă (coloana nr.2) și operatorii economici (coloana nr.3).

Cod poziție	Conținutul cerințelor	Răspuns
1	**2**	3
A. Îndeplinirea tuturor criteriilor de selecție impuse		
5A.1	Operatorul economic este în măsură să furnizeze în Sistemul informaţional automatizat „Registrul de stat al achiziţiilor publice” sau prin mijloace electronice, sau dacă e cazul, pe suport de hârtie autorității contractante: formularele, certificatele, avizele și alte documente indicate de către autoritatea/entitatea contractantă în anunțul de participare și în documentația de atribuire? În termen de **3 zile** de la solicitare. *Notă. Numărul de zile se indică de către autoritatea contractantă ținând cont de cantitatea și caracterul documentelor solicitate.*	☒ Da Nu
5A.2	Informațiile care să îi permită autorității/entității contractante să obțină documentele indicate în anunțul de participare și în documentația de atribuire, sunt disponibile gratuit și direct prin accesarea unei baze de date naționale în orice stat? Dacă da, specificați informația care ar permite verificarea.	Adresa de internet: |text|
		Autoritatea sau organismul emitent(ă) |text|
		Referința exactă a documentației: |text|

Capitolul VI. Preselecția candidaților pentru procedura de atribuire a contractului de achiziție publică

Compartimentul se solicită de către autoritatea contractantă doar în cadrul procedurilor de achiziție publică: licitația restrânsă, negociere, dialog competitiv și parteneriatul pentru inovare.

Cod poziție	Conținutul cerințelor	Răspuns
1	**2**	**3**
A. Îndeplinirea tuturor criteriilor de selecție impuse		
6A.1	Operatorul economic/candidatul îndeplinește criteriile de selecție stabilite de către autoritatea contractantă în anunțul de participare și în documentația de atribuire.	Da Nu ☒
6A.2	Operatorul economic/candidatul dispune și este în măsură să furnizeze în Sistemul informațional automatizat „Registrul de stat al achizițiilor publice” sau prin mijloace electronice, sau dacă e cazul, pe suport de hârtie autorității contractante certificate sau alte forme de documente justificative, după cum este cerut în anunțul de participare și în documentația de atribuire.	☒ Da Nu

Capitolul VII. Declarații finale

Operatorul economic declară că informațiile prezentate în capitolele II – V (după caz II-VI) sunt exacte și corect furnizate, cunoscând pe deplin consecințele cazurilor grave de declarații false.
Operatorul economic declară în mod oficial, că poate să furnizeze la solicitarea autorității/entității contractante fără întârziere, certificatele și documentele justificative solicitate, cu excepția cazului în care autoritatea/entitatea contractantă are posibilitatea de a obține documentele justificative în cauză direct prin accesarea unei baze de date relevante, care este disponibilă gratuit, cu condiția că operatorul economic să fi furnizat informațiile necesare (adresa de internet, autoritatea sau organismul

emitent(ă), referința exactă a documentației) care să îi permită autorității contractante sau entității contractante să facă acest lucru și se consimte accesul la informațiile menționate, în cazul în care acest lucru este necesar.

Operatorul economic declară în mod oficial că este de acord ca **CENTRUL PENTRU ACHIZITII PUBLICE CENTRALIZATE IN SANATATE**, astfel cum este descrisă în capitolul I secțiunea A să obțină acces la documentele justificative privind informațiile pe care le-a furnizat în acest DUAE în scopul desfășurării procedurii de achiziție [ocds-b3wdp1-MD-1732642177049].
(Se va completa și semna de către operatorul economic)

Nume: Vlad Chitic
Funcția: Director executiv
Data: 11.12.2024
Adresa: sos. Muncesti 167/B, mun. Chisinau, Republica Moldova
Semnătura

I.P. "AGENȚIA SERVICII PUBLICE"
Departamentul înregistrare și licențiere a unităților de drept

Extras
din Registrul de stat al persoanelor juridice
nr. **119749** din **02.11.2023**

Denumirea completă: **Societatea cu Răspundere Limitată "LISMEDFARM"**
Denumirea prescurtată: **"LISMEDFARM" S.R.L.**
Forma juridică de organizare: **Societate cu răspundere limitată**
Numărul de identificare de stat și codul fiscal: **1003600113573**
Data înregistrării de stat: **07.12.2001**
Sediu: **MD-2002, Şoseaua Munceşti 167/B, mun. Chişinău, Republica Moldova**
Genurile de activitate:

1. **Comerţul cu ridicata al produselor farmaceutice;**
2. **Comerţul cu amănuntul al produselor farmaceutice şi de parfumerie;**
3. **Comerţul cu ridicata al parfumurilor şi produselor cosmetice;**
4. **Importul, fabricarea, comercializarea, asistenţa tehnică şi (sau) reparaţia dispozitivelor medicale şi (sau) a opticii;**
5. **Comerţul cu ridicata al produselor alimentare, băuturilor şi produselor din tutun;**
6. **Comerţul cu amănuntul neefectuat prin magazine;**
7. **Intermedieri pentru vînzarea unui asortiment larg de mărfuri;**
8. **Comerţul cu ridicata al mărfurilor nealimentare de larg consum;**
9. **Activităţi de cercetare a pieţei şi de sondaj al opiniei publice;**
10. **Publicitate;**
11. **Comerţ cu ridicata cu cafea, ceai, cacao şi condimente;**
12. **Comerţ cu amănuntul al articolelor medicale şi ortopedice, în magazine specializate;**
13. **Comerţ cu amănuntul al produselor cosmetice şi de parfumerie, în magazine specializate;**
14. **Comerţ cu amănuntul al produselor alimentare, băuturilor şi produselor din tutun efectuat prin standuri, chioşcuri şi pieţe;**

Capitalul social: **918180 Lei**
Administrator(i): **CHITIC ECATERINA**
Asociați:

1. **CHITIC ECATERINA, partea socială 918180 Lei, ce constituie 100%**

Beneficiari efectivi: **CHITIC ECATERINA**

Prezentul extras este eliberat în temeiul art. 34 al Legii nr.220/2007 privind înregistrarea de stat a persoanelor juridice şi a întreprinzătorilor individuali şi confirmă datele din Registrul de stat la data de 02.11.2023

Specialist coordonator
Elena Clichici
tel. 022-207832

ORDIN DE PLATA **Nr.** 2648 DATA EMITERII 12 decembrie 2024 TIP DOC : 1

PLATITI: 64391-00 LEI sase zeci si patru mii trei sute noua zeci si unu lei .00 bani

PLATITOR (R) "LISMEDFARM" SRL CODUL IBAN: MD73EX0000000222401475MD

COD FISCAL: 1003600113573

PRESTATORUL PLATITOR: B.C. "EXIMBANK" S.A. SUCURSALA NR.20 CHISINAU

BENEFICIAR (R) MF-TT CHISINAU-BUGETUL DE STAT CENTRUL PENTRU ACHIZITII CENTRALIZATE IN SANATATE CODUL IBAN: MD23TRPCCC518430B01859AA

COD FISCAL: 1016601000212

PRESTATORUL BENEFICIAR: MINISTERUL FINANTELOR - TREZORERIA DE STAT

DESTINATIA PLATII

/P102/64391,00 Plata pentru Garantia pentru oferta la LP nr. ocds-b3wdp1-MD-1732642177049 din 12.12.2024

TIPUL TRANSFERULUI NORMAL/URGENT

N

L.S.

COD TRANZACTIE: 101

DATA PRIMIRII: 12 decembrie 2024

DATA EXECUTARII: 12 decembrie 2024 08:57:52

SEMNATURA BANCII: 087F2A4746BD486192562AED096A21DD

SEMNATURA BANCII

SEMNATURILE EMITENTULUI

ECATERINA CHITIC
NS/Fg37L06/i057bCZ/7UKHIhZRM+gr4SYdMAsw=
ECATERINA CHITIC
NS/Fg37L06/i057bCZ/7UKHIhZRM+gr4SYdMAsw=

Inițiat în sistemul Eximbank Online și autorizat cu Semnătura Digitală

MOTIVUL REFUZULUI:

REPUBLICA MOLDOVA

LICENȚĂ

Seria A MMI **Nr. 002359**

Denumirea autorității de licențiere	Agenţia Medicamentului şi Dispozitivelor Medicale
Denumirea, forma juridică de organizare, adresa juridică a titularului de licență/ Numele, prenumele şi adresa persoanei fizice	**"LISMEDFARM S.R.L."** Republica Moldova, mun. Chişinău, sec. Botanica, str-la Munceşti, 167, bloc. B
Data adoptării deciziei de înregistrare a titularului de licență	**07.12.2001**
Numărul de identificare de stat al unității de drept (IDNO)/Numărul de identificare de stat al persoanei fizice (IDNP)	**1003600113573**
Genul de activitate	**Activitatea farmaceutică**
Data eliberării/prelungirii licenței	**19.02.2024**
Valabilă până la	**18.02.2029**
Semnătura conducătorului autorității de licențiere	**Lina Gudima** *semnat electronic*

L.Ș.

Notă: Licența este valabilă numai cu anexa autentificată de autoritatea de licențiere, în care sunt indicate condițiile de licențiere pentru genul de activitate specificat în licență.

ANEXĂ LA LICENȚA

Seria A MMI Nr. 002359

Titularul de licență **“LISMEDFARM S.R.L.”**

Titularul de licență este obligat să respecte următoarele condiții de licențiere pentru desfășurarea activității:

Condiţii de licenţiere:

Asigurarea informării consumatorilor în mod complet, corect și precis asupra caracteristicilor produselor farmaceutice, privind calitatea şi inofensivitatea medicamentelor (Art. 24 al Legii nr. 105-XV din 13.03.2003 privind protecţia consumatorilor, Art.18 al Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Asistenţa cu medicamente de bună calitate. Medicamentele și produsele parafarmaceutice eliberate populației trebuie să corespundă cerinţelor Farmacopeei sau altei documentaţii tehnico-normative aprobate de Ministerul Sănătății (Art. 18 alin. (3) al Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Cetăţenii străini și apatrizii care au studii farmaceutice pot exercita activitatea farmaceutică, după echivalarea și recunoașterea documentelor de studii în modul stabilit de lege, în aceleași condiții ca și cetățenii Republicii Moldova (Art. 22 alin. (3) al Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Depozitele farmaceutice, farmaciile şi filialele acestora sînt conduse numai de farmaciști. Ca excepţie, farmaciile și filialele farmaciilor amplasate în localităţile rurale pot fi conduse de laboranți-farmaciști care au calificarea corespunzătoare cerinţelor stabilite de Ministerul Sănătății (Art. 22 alin. (2) al Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Desfășurarea activității licențiate în conformitate cu cadrul legislativ și normativ (Legea nr. 160 din 22.07.2011 privind reglementarea prin autorizare a activității de întreprinzător; Legea nr. 1456 din 25.05.1993 cu privire la activitatea farmaceutică,);

Dispunerea de spaţii pentru desfășurarea activității licentiate ce le aparţin cu drept de proprietate privată sau în alte spaţii luate în locaţiune, inclusiv ale instituţiilor medico-sanitare publice, cu gen de activitate în domeniul ocrotirii sănătății, care corespund cerinţelor actelor legislative şi normative în vigoare privind parteneriatul public-privat (Art. 4 alin.(4) al Legii ocrotirii sănătății nr. 411-XIII din 28.03.1995);

Distribuirea angro a medicamentelor se efectuează prin intermediul întreprinderilor autohtone de producţie farmaceutică, laboratoarelor de microproducţie și depozitelor farmaceutice care deţin licenţa respectivă, eliberată în conformitate cu legislaţia în vigoare (Art. 201 alin. (2) al Legii nr. 1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Distribuirea cu amănuntul a medicamentelor se efectuează prin intermediul farmaciilor comunitare care deţin licenţa respectivă, eliberată în conformitate cu legislaţia în vigoare (Art. 201 alin. (3) al Legii nr. 1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Eliberarea substanţelor stupefiante și psihotrope pentru consum individual numai cu reţete medicale speciale (Art. 15 alin. (1) al Legii nr. 382-XIV din 06.05.1999 cu privire la circulaţia substanţelor stupefiante, psihotrope și a precursorilor);

Exercitarea activității farmaceutice de către specialiști cu studii farmaceutice superioare sau medii și calificarea corespunzătoare cerinţelor stabilite de Ministerul Sănătății; în instituţiile medico-sanitare publice din localităţile rurale, în care nu există asistență farmaceutică, activitatea farmaceutică în cadrul filialelor de categoria a II-a ale farmaciilor, ca excepţie, poate fi exercitată de lucrători medicali care posedă cunoştinţe practice în domeniul farmaceutic (Art. 22 alin. (1) şi (21) și Art. 27 alin. (1) ale Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceut

Farmaciile (filialele) nou-fondate vor fi amplasate la o distanță de cel puţin 250 de metri (cale accesibilă) de la farmacia (filiala) existentă şi la o distanță de cel puţin 500 de metri (cale accesibilă) de la farmacia existentă cu funcţie de preparare a medicamentelor extemporale (Art. 19 alin. (4) al Legii nr. 1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Farmaciile nou-fondate vor fi înființate conform Planului Naţional de Amplasare a Farmaciilor (Art. 19 alin. (6) al Legii nr. 1456-XII din 25.05.1993 cu privire la activitatea farmaceutică).

În municipii, orașe, centre raionale și alte localități cu statut de oraș o farmacie se înființează la un număr de la 3000 pînă la 4000 de locuitori (Art. 19 alin. (5) al Legii nr. 1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Instituţiile și întreprinderile farmaceutice de stat și private sînt supuse evaluării și acreditării, în mod obligatoriu, o dată în 5 ani (Art. 11 alin. (1) al Legii nr. 552-XV din 18.10.2001 privind evaluarea și acreditarea în sănătate);

Neadmiterea comercializării medicamentelor fără reflectarea circuitului acestora în sistemul informaţional automatizat de evidenţă a circulaţiei medicamentelor (Art. 20^1 alin. (4) al Legii nr. 1456-XII din 25.05.1993 cu privire la activitatea farmaceutică; Hotărîrea Guvernului nr. 85 din 25.01.2006 cu privire la implementarea Sistemului informaţional automatizat „Nomenclatorul de stat al

medicamentelor");

Neadmiterea conducerii prin cumul a întreprinderii şi/sau instituţiei farmaceutice de către farmacist (diriginte) şi laborant-farmacist (şef de filială). Neadmiterea conducerii prin cumul a unităţii farmaceutice de către farmacist (laborant-farmacist) Art.143 lit. e) şi Art. 22 alin.(4) ale Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceutică.

Neadmiterea producerii, depozitării şi comercializării medicamentelor falsificate (contrafăcute) şi cu termenul de valabilitate expirat (Art. 6 alin. (4) şi (7) al Legii nr.105-XV din 13.03.2003 privind protecţia consumatorilor);

Respectarea cerinţelor de formare a preţurilor la medicamente, alte produse farmaceutice (Art. 20 alin. (1) şi (2) al Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceutică; Hotărîrea Guvernului nr. 603 din 02.07.1997 despre aprobarea Regulamentului privind formarea preţurilor la medicamente, articole de uz medical şi alte produse farmaceutice);

Respectarea cerinţelor tehnice faţă de încăperile şi obiectivele în care se păstrează substanţe stupefiante, psihotrope şi/sau precursori (Hotărîrea Guvernului nr. 128 din 06.02.2006 cu privire la aprobarea Cerinţelor tehnice faţă de încăperile şi obiectivele în care se păstrează substanţe stupefiante, psihotrope şi/sau precursori);

Respectarea regulilor şi normativelor privind spaţiul, amplasarea şi dotarea încăperilor unităţii farmaceutice, regimului sanitaro-epidemiologic şi a securităţii antiincendiare (Hotărârea Guvernului nr. 504 din 12.07.2012 pentru aprobarea Regulamentului sanitar privind dotarea şi exploatarea farmaciilor şi depozitelor farmaceutice; Art. 7 al Legii nr. 845-XII din 03.01.1992 cu privire la antreprenoriat şi întreprinderi; Art. 10 lit.a);

Un farmacist (laborant-farmacist) poate să conducă numai o unitate farmaceutică (Art. 22 alin. (4) al Legii nr.1456-XII din 25.05.1993 cu privire la activitatea farmaceutică);

Adresa de desfasurare a activitatii:

Adresa: Sub genuri de activitate

1. **mun. Chişinău, sec. Botanica, şos. Munceşti, 167, bloc. b** farmacist-diriginte:Chitic Ecaterina, în cadrul depozitului farmaceutic

- **- inclusiv cu dreptul de activitate cu substanțe stupefiante, psihotrope și precursori**

1. mun. Chișinău, str. Munceşti, 167/B, farmacist-diriginte: Chitic Ecaterina; în cadrul depozitului farmaceutic, inclusiv cu dreptul de achiziționare, păstrare şi eliberare a preparatelor stupefiante, psihotrope și precursori;
2. mun. Chişinău, str. Miron Costin, 7; farmacist-diriginte: Meachişeva Alla; în cadrul farmaciei de forme industriale, inclusiv cu dreptul de achiziționare, păstrare şi eliberare a preparatelor stupefiante, psihotrope și precursori;

3. mun. Chişinău, bd. Cuza-Vodă, 30/1; şef de filială: Barda Vladimir; filiala farmaciei de forme industriale, inclusiv cu dreptul de achiziționare, păstrare şi eliberare a preparatelor psihotrope și precursori;

4. mun. Chişinău, str. Munceşti, 167/B; şef de filială: Iscra Natalia; filiala de categoria I a farmaciei de forme industriale, inclusiv cu dreptul de achiziționare, păstrare şi eliberare a preparatelor stupefiante, psihotrope și precursori;

5. r-l Sîngerei, s. Prepelița, şef de filială: Novoloaca Ana; filiala de categoria II a farmaciei de forme industriale, cu excepția dreptului de achiziționare, păstrare şi eliberare a preparatelor stupefiante, psihotrope și precursori;

6. or. Râșcani, str. 31 August, 1989, 16, bloc A; şef de filială: Gaidău Ecaterina; filiala de categoria I a farmaciei de forme industriale, inclusiv cu dreptul de achiziționare, păstrare şi eliberare a preparatelor psihotrope și precursori.

7. mun. Chișinău, str. Butucului, 14, şef de filială: Fratovcean Ludmila, în cadrul filialei de farmacie de forme industriale, inclusiv cu dreptul de achiziționare, păstrare și eliberare a preparatelor psihotrope și precursori.

LISMEDFARM S.R.L.
Șos. Munceşti, 167/B, MD – 2002, mun. Chișinău, Republica Moldova
c/f: 1003600113573, TVA: 0304618, web: https://lismedfarm.md,
tel.: 022-80-47-98, 022-55-64-38, 022-56-94-91, e-mail: oficiu@lismedfarm.md

Număr B-012/2021 din 22.04.2021 **Către:** TOATE PERSOANELE INTERESATE

Lista Fondatorilor

Chitic Ecaterina Nicolai, anul nașterii: 30 decembrie 1969, cetățean al Republicii Moldova (MD), cod personal: 0970808153221.

Cotă: 100%

Cu respect,
Directorul companiei "Lismedfarm" SRL, Ecaterina Chitic

Ex.: Vlad Chitic
Director executiv
+373 799 81 005
vlad.chitic@lismedfarm.md

Hessian Office For Health And Care

CERTIFICATE NUMBER: ***DE_HE_01_GMP_2023_0234***

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER [1,2]

Part 1

Issued following an inspection in accordance with
Art. 111(5) of Directive 2001/83/EC as amended
Art. 63 of Regulation (EU) 536/2014 as amended

The competent authority of Germany confirms the following:
The manufacturer: ***Lupin Limited***
Site address: ***Unit 1 Plot No 6A1 6A2 Sector 17, Special Economic Zone, Mihan, Nagpur, 441108, India***
OMS Organisation Id. / OMS Location Id.: ***ORG-100004130*** / ***LOC-100053222***
DUNS Number: ***65-075-9348***

Has been inspected in connection with marketing authorisation(s) listing manufacturers located outside of the European Economic Area in accordance with Art. 8(2) of Regulation (EC) 726/2004 and Art. 111(4) of Directive 2001/83/EC.

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2023-06-23***, it is considered that it complies with::

- The principles and guidelines of Good Manufacturing Practice laid down in Directive (EU) 2017/1572 and/or Commission Delegated Regulation (EU) 2017/1569, as reflected by the product categories stated in Part 2.[3]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. Updates to restrictions or clarifying remarks can be identified through the EudraGMDP website (http://eudragmdp.ema.europa.eu/). This certificate is valid only when presented with all pages and both Parts 1 and 2.

The authenticity of this certificate may be verified in EudraGMDP. If it does not appear, please contact the issuing authority.

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[1] *The certificate referred to in paragraph Art. 111(5) of Directive 2001/83/EC and Art. 15 of Directive 2001/20/ECis also applicable to importers.*

[2] *Guidance on the interpretation of this template can be found in the Interpretation of the Union format for GMP certificate.*

[3] *These requirements fulfil the GMP recommendations of WHO.*

Part 2

Human Medicinal Products Human Investigational Medicinal Products

1 MANUFACTURING OPERATIONS	
1.2	**Non-sterile products**
	1.2.1 Non-sterile products (processing operations for the following dosage forms) 1.2.1.8 Other solid dosage forms 1.2.1.13 Tablets
1.5	**Packaging**
	1.5.1 Primary Packaging 1.5.1.8 Other solid dosage forms 1.5.1.13 Tablets
	1.5.2 Secondary packaging
1.6	**Quality control testing**
	1.6.2 Microbiological: non-sterility *1.6.3 Chemical/Physical*

Clarifying remarks (for public users)

Ref. to 1.2.1.8 and 1.5.1.8: Powder for oral application. Ref. to 1.2.1.13, 1.5.1.13 and 1.5.2: Including film-coated tablets. Ref. to 1.6.2 and 1.6.3: On-Going-Stability tests. scope of inspection: - Apixaban Hormosan 2,5 mg film-coated tablets - Apixaban Hormosan 5 mg film-coated tablets - Raltegravir 600 mg film-coated tablets - Mexiletine Hydrochloride Extended Release Powder for Oral Suspension 200 mg (Investigational medicinal product) - Mexiletine Hydrochloride Extended Release Powder for Oral Suspension 600 mg (Investigational medicinal product) This certificate is in case of importation int the European Union only valid in connection with the current confirmation acording to para 72a section 1 sentence 1 number 2 Medicinal Products Avt, the German Drug Law (Arzneimittelgesetz AMG), issued to the importing company Hormosan Pharma GmbH, after the inspection according to para 72a section 1 sentence 2 number 1 Medicinal Products Act, and after confirming the (text missing)

2023-11-08

Name and signature of the authorised person of the Competent Authority of

---

Confidential
Regierungspraesidium Darmstadt
Tel:***Confidential***
Fax:***Confidential***

NDA 214544

TENTATIVE APPROVAL

Lupin Pharmaceuticals, Inc.
U.S. Agent for Lupin Limited, India
Attention: Mr. Debashis Mohanty
Associate Director - Regulatory Affairs
111 South Calvert Street
Harborplace Tower, 21st Floor
Baltimore, MD 21202

Dear Mr. Mohanty:

Please refer to your new drug application (NDA) dated and received April 9, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (FD&C Act) for the following drug product:

- Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets, 50 mg/200 mg/25 mg

We acknowledge receipt of your amendment dated July 19, 2022, which constituted a complete response to our September 16, 2021, complete response letter. The September 16, 2021, complete response letter was issued due to deficiencies concerning the reliability and validity of bioequivalence data generated from studies conducted by Panexcell Clinical Lab Pvt. Ltd. which were submitted to FDA in support of your NDA.

This NDA provides for the use of Dolutegravir, Emtricitabine, and Tenofovir Alafenamide Tablets as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 25 kg.

This NDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR).

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105(a); therefore, it is not approved and will not be approved until FDA issues an approval after any necessary additional review of the NDA. Enclosed is the tentatively approved submitted labeling (Prescribing Information submitted January 18, 2023, Patient Package Insert submitted January 18, 2023, container labeling submitted January 13, 2023) with minor revisions listed below. Based on the data provided, the expiration dating period is 36 months for Dolutegravir, Emtricitabine, and Tenofovir Alafenamide Tablets, 50 mg/200 mg/25 mg in HDPE bottles containing 30, 60 or 90 tablets with desiccant and child-resistant cap when

stored below 30ºC (86ºF). Also, HDPE bottles containing 1,000 tablets with desiccant and non-child-resistant cap (for repacking within 6 months) stored below 30ºC (86ºF) are included in this action.

Minor Revisions for the Prescribing Information

1. FPI, 2 DOSAGE AND ADMINISTRATION, 2.5 Not Recommended in Patients With Severe Hepatic Impairment: Changed the numbering to "2.4"
2. FPI, 2 DOSAGE AND ADMINISTRATION, 2.5 Not Recommended in Patients With Severe Hepatic Impairment: Italicized the reference "[see Use in Specific Populations (8.7)]"
3. FPI, 16 HOW SUPPLIED/STORAGE AND HANDLING: Added "… and supplied as follows:"

This tentative approval determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application may not be granted before the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the patent(s) and/or exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling and chemistry, manufacturing, and controls data. This amendment should include draft final printed labels and labeling which comply with all U.S. regulations (uniqueness of drug product appearance per 21 CFR 206; child-resistant packaging per 16 CFR 1700, etc.). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

This drug product is not approved and cannot be legally marketed in the United States until you have been notified in writing that this NDA is approved. The use of the enclosed tentatively approved labeling is not permitted for U.S. marketing this drug product.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labeling must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names (*April 2016)[1]*,* guidance for industry *Best Practices in Developing Proprietary Names for Human Prescription Drug Products* (December 2020), and *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022*.)[2]

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

OTHER

We also remind you that you are expected to comply with the reporting requirements provided in 21 CFR 314.80 and 314.81. If the product is to be mass distributed in developing countries, a system of collecting and reporting adverse drug reactions by the distributor would be desirable (e.g., through governmental or nongovernmental agencies distributing the products).

If you have any questions, call Monica Zeballos, Pharm.D., Sr. Program Consultant, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Sarita Boyd, Pharm.D.
Associate Director for PEPFAR
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[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] https://www.fda.gov/media/151712/download

Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S): (tentatively approved)

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR ALAFENAMIDE TABLETS safely and effectively. See full prescribing information for DOLUTEGRAVIR, EMTRICITABINE AND TENOFOVIR ALAFENAMIDE TABLETS.

DOLUTEGRAVIR, EMTRICITABINE and TENOFOVIR ALAFENAMIDE tablets, for oral use

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B

See full prescribing information for complete boxed warning.

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF) and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Hepatic function should be monitored closely in these patients. If appropriate, anti-hepatitis B therapy may be warranted. (5.1)

---------- INDICATIONS AND USAGE ----------

Dolutegravir, emtricitabine and tenofovir alafenamide tablets, a three-drug combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), emtricitabine (FTC) and tenofovir alafenamide (TAF), both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs), is indicated as a complete regimen for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 25 kg. (1)

Limitations of Use:

- Dolutegravir, emtricitabine and tenofovir alafenamide tablets alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, emtricitabine and tenofovir alafenamide tablets is insufficient in these subpopulations. See the dolutegravir prescribing information. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Pregnancy Testing: Pregnancy testing is recommended before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential. (2.1, 5.4)
- Testing: Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets, test for hepatitis B virus infection. Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets and during treatment, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. (2.1)
- Recommended dosage: One tablet taken once daily in adults and pediatric patients weighing at least 25 kg. May be taken with or without food. (2.2)
- Renal Impairment: Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 30 mL per minute. (2.3)

----------DOSAGE FORMS AND STRENGTHS ----------

Tablets: 50 mg of dolutegravir, 200 mg of emtricitabine and 25 mg of tenofovir alafenamide (3)

---------- CONTRAINDICATIONS ----------

- Previous hypersensitivity reaction to dolutegravir. (4)
- Coadministration with dofetilide. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop. (5.2)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Assess the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception. (2.1, 5.4, 8.1, 8.3)
- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.6)
- New onset or worsening renal impairment: Assess creatinine clearance, estimated creatinine clearance, urine glucose, and urine protein when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets and during use on a clinically appropriate schedule in all patients. Also assess serum phosphorus in patients with chronic kidney disease. (5.7)
- Lactic acidosis/severe hepatomegaly with steatosis: Discontinue treatment in patients who develop symptoms or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity. (5.8)

---------- ADVERSE REACTIONS ----------

- Dolutegravir: The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving dolutegravir in any one adult trial) are insomnia, fatigue, headache and diarrhea. (6.1)
- Emtricitabine and Tenofovir Alafenamide: Most common adverse reaction (incidence greater than or equal to 10% all grades) is nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of dolutegravir, emtricitabine and tenofovir alafenamide tablets. The potential drug-drug interactions must be considered prior to and during therapy. (4, 7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Assess the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester or if pregnancy is confirmed in the first trimester due to the risk of neural tube defects. (2.1, 5.4, 8.1, 8.3)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing is recommended in adolescents and adults of childbearing potential. Patients should be counseled on the consistent use of effective contraception. (8.1, 8.3)
- Hepatic impairment: Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with severe hepatic impairment (Child-Pugh Score C). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: POST-TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B virus (HBV) have been reported in HBV-infected patients who have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are infected with HBV and discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets. If appropriate, anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and pediatric patients weighing at least 25 kg.

Limitations of Use:

- Dolutegravir, emtricitabine and tenofovir alafenamide tablets alone is not recommended in patients with resistance-associated integrase substitutions or clinically suspected integrase strand transfer inhibitor resistance because the dose of dolutegravir in dolutegravir, emtricitabine and tenofovir alafenamide tablets is insufficient in these subpopulations. See the dolutegravir prescribing information.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation and During Treatment With Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets

Pregnancy testing is recommended before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential [s*ee Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)*].

Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets, test patients for hepatitis B virus (HBV) infection [see *Warnings and Precautions (5.1)]*.

Prior to initiation and during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets, on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

2.2 Recommended Dosage in Adults and Pediatric Patients Weighing at Least 25 kg (55 lbs)

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a three-drug fixed-dose combination product containing 50 mg of dolutegravir, 200 mg of emtricitabine (FTC) and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of dolutegravir, emtricitabine and

tenofovir alafenamide tablets is one tablet taken orally once daily with or without food in adults and pediatric patients weighing at least 25 kg (55 lbs) and creatinine clearance greater than or equal to 30 mL per minute.

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg.

2.3 Not Recommended in Patients With Severe Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 30 mL per minute *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.*6)]

2.4 Not Recommended in Patients With Severe Hepatic Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with severe hepatic impairment (Child-Pugh Score C) *[see Use in Specific Populations (8.7)]*.

3 DOSAGE FORMS AND STRENGTHS

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are white to off-white colored, modified capsule shaped, film-coated tablets, debossed with "L6" on one side and "L" on other side, containing 50 mg of dolutegravir (as dolutegravir sodium), 200 mg of emtricitabine and 25 mg of tenofovir alafenamide (as tenofovir alafenamide fumarate).

4 CONTRAINDICATIONS

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir or any of the components of this product *[see Warnings and Precautions (5.2)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of dolutegravir *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Acute Exacerbation of Hepatitis B in Patients with HBV Infection

All patients should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Dosage and Administration (2.1)]*.

Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in HBV-infected patients who have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Patients infected with HBV who discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure. HBV-uninfected patients should be offered vaccination.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with the use of dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and were characterized by rash, constitutional findings and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving dolutegravir in Phase 3 clinical trials. Discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. Dolutegravir, emtricitabine and tenofovir alafenamide tablets is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir or any of the components of this product.

5.3 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Adverse Reactions (6.1)]*. In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with fixed-dose abacavir, dolutegravir, and lamivudine. Monitoring for hepatotoxicity is recommended.

5.4 Embryo-Fetal Toxicity

An ongoing observational study showed an association between dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, and an increased risk of neural tube defects when dolutegravir was administered at the time of conception and in early pregnancy. As there is limited understanding of the association of reported types of neural tube defects with dolutegravir use, inform adolescents and adults of childbearing potential, including those actively trying to become pregnant, about the potential increased risk of neural tube defects with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Assess the risks and benefit of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester *[see Use in Specific Populations (8.1, 8.3)]*.

Pregnancy testing is recommended before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets in adolescents and adults of childbearing potential *[see Dosage and Administration (2.1)]*.

Adolescents and adults of childbearing potential should be counseled on the consistent use of effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets may be considered during the second and third trimesters of pregnancy if the expected benefit justifies the potential risk to the pregnant woman and the fetus.

5.5 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of dolutegravir, emtricitabine and tenofovir alafenamide tablets and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]*:

- Loss of therapeutic effect of dolutegravir, emtricitabine and tenofovir alafenamide tablets and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 4 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; review concomitant medications during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets; and monitor for the adverse reactions associated with the concomitant drugs.

5.6 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including dolutegravir and FTC, two components of dolutegravir, emtricitabine and tenofovir alafenamide tablets. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP] or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis and Guillain-Barré) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

5.7 New Onset or Worsening Renal Impairment

Post-marketing cases of renal impairment, including acute renal failure, proximal renal tubulopathy (PRT) and Fanconi syndrome have been reported with TAF-containing products; while most of these cases were characterized by potential confounders that may have contributed to the reported renal events, it is also possible these factors may have predisposed patients to tenofovir-related adverse events *[see Adverse Reactions (6.1, 6.2)]*.

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended in patients with estimated creatinine clearance below 30 mL per minute because data in this population are insufficient.

Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

Prior to or when initiating dolutegravir, emtricitabine and tenofovir alafenamide tablets and during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

5.8 Lactic Acidosis and Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets and tenofovir DF, another prodrug of tenofovir, alone or in combination with other antiretrovirals. Treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

6 ADVERSE REACTIONS

The following serious adverse drug reactions are discussed in other sections of the labeling:

- Severe Acute Exacerbation of Hepatitis B *[see Boxed Warning and Warnings and Precautions (5.1)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.6)]*.
- New Onset or Worsening Renal Impairment *[see Warnings and Precautions (5.7)]*.
- Lactic Acidosis and Severe Hepatomegaly with Steatosis *[see Warnings and Precautions* (5.8)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug (or a drug given in various combinations with other concomitant therapy) cannot be directly compared to rates in the clinical trials of another drug (or a drug given in the same or different combination therapy) and may not reflect the rates observed in practice.

Clinical Trials Experience in Adult Subjects

Dolutegravir:

Treatment-Naïve Subjects

The safety assessment of dolutegravir in HIV-1-infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467).

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir DF [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir DF (ATRIPLA) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving dolutegravir 50 mg once daily + fixed-dose abacavir and lamivudine (EPZICOM) and 14% in subjects receiving fixed-dose efavirenz/emtricitabine/tenofovir DF (ATRIPLA) once daily.

Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in dolutegravir treatment arm in either SPRING-2 or SINGLE were insomnia (3%), headache (2%), and fatigue (2%).

In addition, Grade 1 insomnia was reported by 1% and less than 1% of subjects receiving dolutegravir and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for dolutegravir and fixed-dose efavirenz/emtricitabine/tenofovir DF (ATRIPLA), respectively. These events were not treatment limiting.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects
In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV-1-infected, antiretroviral treatment-experienced adults were randomized and received either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving dolutegravir 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent adverse reaction of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving dolutegravir 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials
The following ARs occurred in less than 2% of treatment-naïve or treatment-experienced subjects receiving dolutegravir in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders:
Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary Disorders:
Hepatitis.

Musculoskeletal Disorders:
Myositis.

Psychiatric Disorders:
Suicidal ideation, attempt, behavior or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders:
Renal impairment.

Skin and Subcutaneous Tissue Disorders:
Pruritus.

Laboratory Abnormalities
Treatment-Naïve Subjects:
Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects are presented in Table 1. The mean change from baseline observed for selected lipid values is presented in Table 2. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 1: Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		SINGLE	
Laboratory Parameter Preferred Term	**Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**Dolutegravir 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)**	**Efavirenz, Emtricitabine and Tenofovir DF Once Daily (n = 419)**
ALT				
Grade 2 (>2.5-5.0 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (>5.0 x ULN)	2%	2%	1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (>5.0 x ULN)	3%	2%	1%	3%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	3%	2%	<1%	<1%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	<1%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	4%	7%	8%

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz, Emtricitabine and Tenofovir DF Once Daily (n = 419)
Hyperglycemia				
Grade 2 (126-250 mg/dL)	6%	6%	9%	6%
Grade 3 (>250 mg/dL)	<1%	2%	2%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	7%	7%	11%	11%
Grade 3 to 4 (>3.0 x ULN)	2%	5%	5%	4%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	4%	3%	4%	5%
Grade 3 to 4 (<0.75 x 10^9)	2%	2%	3%	3%

ALT = Alanine aminotransferase; AST =Aspartate aminotransferase; ULN = Upper limit of normal.

Table 2: Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis[a]) and SINGLE Trials (Week 144 Analysis[a])

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	Dolutegravir 50 mg Once Daily + 2 NRTIs (n = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)	Dolutegravir 50 mg + Abacavir Sulfate and Lamivudine Once Daily (n = 414)	Efavirenz, Emtricitabine, and Tenofovir DF Once Daily (n = 419)
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2
LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

HDL = high density lipoprotein; LDL = low density lipoprotein.

[a] Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 30 and fixed-dose efavirenz/emtricitabine/tenofovir df n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless of whether they discontinued the agent (SPRING-2: dolutegravir n = 9, raltegravir n = 13; SINGLE: dolutegravir + fixed-dose abacavir sulfate and lamivudine n = 36, fixed-dose efavirenz/emtricitabine/tenofovir n = 36).

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Hepatitis B and/or Hepatitis C Virus Co-infection

In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the upper limit of normal. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co-infection for all

treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving dolutegravir were observed in 18% vs. 3% with the 50 mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with dolutegravir, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Warnings and Precautions (5.3)]*.

Changes in Serum Creatinine
Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

FTC and TAF:
Adverse Reactions in Clinical Trials of FTC + TAF with Elvitegravir (EVG) plus Cobicistat (COBI) in Treatment-Naïve Adults with HIV-1 Infection
In pooled 48-week trials of antiretroviral treatment-naïve HIV-1-infected adult subjects, the most common adverse reaction in subjects treated with FTC + TAF with EVG + COBI (N = 866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group, 0.9% of subjects discontinued FTC + TAF with EVG + COBI due to adverse events during the 48-week treatment period *[see Clinical Studies (14)]*. The safety profile was similar in virologically-suppressed adults with HIV-1 infection who were switched to FTC + TAF with EVG + COBI (N = 799). Antiretroviral treatment-naïve adult subjects treated with FTC + TAF with EVG + COBI experienced mean increases of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol and 29 mg/dL of triglycerides after 48 weeks of use.

Renal Laboratory Tests
In two 48-week trials in antiretroviral treatment-naïve HIV-1-infected adults treated with FTC + TAF with EVG + COBI (N = 866) with a median baseline eGFR of 115 mL per minute, mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. Median urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to FTC + TAF with EVG + COBI (N = 959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline at Week 48; median UPCR was 61 mg per gram at baseline and 46 mg per gram at Week 48. Across these trials, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with FTC+TAF with EVG+COBI.

In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC + TAF with EVG + COBI (N = 248), mean serum creatinine was 1.5 mg per dL at both baseline and Week 24. Median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24. FTC+TAF with EVG+COBI was permanently discontinued due to worsening renal function in two of 80 (3%) subjects.

Bone Mineral Density Effects
In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1-infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 -1.30% with FTC + TAF with EVG + COBI at the lumbar spine and -0.66% at the total hip. BMD declines of 5% or greater at the lumbar spine were experienced by 10% of FTC + TAF with EVG + COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 7% of FTC + TAF with EVG + COBI subjects. The long-term clinical significance of these BMD changes is not known.

In 799 virologically-suppressed TDF-treated adult subjects that switched to FTC + TAF with EVG + COBI, at Week 48 mean BMD increased (1.86% lumbar spine, 1.95% total hip). BMD declines of 5% or greater at the lumbar spine were experienced by 1% of FTC + TAF with EVG + COBI subjects. BMD declines of 7% or greater at the femoral neck were experienced by 1% of FTC + TAF with EVG + COBI subjects.

Clinical Trials Experience in Pediatric Subjects
Dolutegravir:
The safety and pharmacokinetics of dolutegravir in HIV-1-infected pediatric subjects was evaluated in the IMPAACT P1093 trial and weight-band-based pharmacokinetic substudies of the ODYSSEY trial. IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of HIV-1-infected pediatric subjects aged 4 weeks to less than 18 years *[see Clinical Studies (14.2)]*. ODYSSEY is an ongoing open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and pharmacokinetic parameters of dolutegravir plus two NRTIs compared with standard of care in HIV-1-infected pediatric subjects younger than 18 years. Overall, the safety data in these pediatric studies were similar to those seen in adults, and there was no clinically significant difference in dolutegravir exposure *[see Clinical Pharmacology (12.3)]*.

FTC and TAF:
The safety profile of FTC+TAF in pediatric subjects weighing at least 25 kg is informed by an open-label trial of antiretroviral treatment-naïve HIV-1 infected pediatric subjects between the ages of 12 to less than 18 years weighing at least 35 kg through 48 weeks (N=50; Cohort 1) and virologically-suppressed subjects between the ages of 6 to less than 12 years weighing at least 25 kg (N=52; Cohort 2). Subjects received FTC+TAF with EVG+COBI through 48 weeks. With the exception of a decrease in the mean CD4+ cell count observed in Cohort 2, the safety of this combination was similar to that in adults.

Bone Mineral Density Effects
Among the subjects in Cohort 1 (*treatment-naïve adolescents 12 to less than 18 years of age and weighing at least 35 kg),* mean BMD increased from baseline to Week 48, +4.2% at the lumbar spine and +1.3% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were −0.07 for lumbar spine and −0.20 for TBLH at Week 48. One subject had significant (at least 4%) lumbar spine BMD loss at Week 48.

Among the subjects in Cohort 2 (*virologically-suppressed children (6 to less than 12 years of age and weighing at least 25 kg),* mean BMD increased from baseline to Week 48, +3.9% at the lumbar

spine and +4.2% for the total body less head (TBLH). Mean changes from baseline BMD Z-scores were -0.24 for lumbar spine and -0.19 for TBLH at Week 48. Six subjects had significant (at least 4%) lumbar spine BMD loss at Week 48 and 2 subjects also had at least 4% TBLH BMD loss at Week 48.

Change from Baseline in CD4+ cell counts
Cohort 2 evaluated pediatric subjects (N=52) who were virologically-suppressed and who switched from their antiretroviral regimen to FTC+TAF with EVG+COBI. Although all subjects had HIV-1 RNA < 50 copies/mL, there was a decrease from baseline in CD4+ cell count at Weeks 24 and 48. The mean baseline and mean change from baseline in CD4+ cell count and in CD4% from Week 2 to Week 48 are presented in Table 3. All subjects maintained their CD4+ cell counts above 400 cells/mm^3.

Table 3: Mean Change in CD4+ Count and CD4 Percentage from Baseline to Week 48 in Virologically-Suppressed Pediatric Patients from 6 to <12 Years Who Switched to FTC+TAF with EVG+COBI

	Baseline	Mean Change from Baseline					
		Week 2	Week 4	Week 12	Week 24	Week 32	Week 48
CD4+ Cell Count (cells/mm^3)	961 (275.5) [a]	-117	-114	-112	-118	-62	-66
CD4%	38 (6.4)[a]	+0.3%	-0.1%	-0.8%	-0.8%	-1.0%	-0.6%

a. Mean (SD)

6.2 Postmarketing Experience
In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dolutegravir
Hepatobiliary Disorders:
Acute liver failure, hepatotoxicity.

Investigations:
Weight increased

Musculoskeletal:
Arthralgia, myalgia.

Psychiatric:
Anxiety.

TAF
Skin and Subcutaneous Tissue Disorders:
Angioedema, urticaria, and rash

Renal and Urinary Disorders:
Acute renal failure, acute tubular necrosis, proximal renal tubulopathy, and Fanconi syndrome

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 microM). *In vivo*, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide, dalfampridine, and metformin, Table 4) *[see Contraindications (4) and Drug Interactions (7.3)]*.

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC_{50} = 2.12 microM) and OAT3 (IC_{50} = 1.97 microM). However, *in vivo*, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC_{50} greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridyl diphosphate glucuronosyl transferase (UGT)1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2 or MRP4. *In vitro*, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir, FTC, or TAF

Dolutegravir

Dolutegravir, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP and P-gp *in vitro*. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir and is expected to be mitigated by atazanavir/ritonavir (Table 4) *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

FTC and TAF

TAF, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption (see Table 4). Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of dolutegravir, emtricitabine and tenofovir alafenamide tablets and development of resistance. Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with other drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentration of TAF. TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*. TAF is not an inhibitor or inducer of CYP3A *in vivo*.

7.3 Established and Other Potentially Significant Drug Interactions

There were no drug interaction trials conducted with dolutegravir and fixed-dose emtricitabine and tenofovir alafenamide or with the fixed-dose combination of all three components.

Information regarding potential drug interactions with dolutegravir, emtricitabine and tenofovir alafenamide (Table 4) are provided below.

These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy *[see Contraindications (4) and Clinical Pharmacology (12,3)]*.

Table 4: Established and Other Potentially Significant Drug Interactions for Dolutegravir, Emtricitabine and Tenofovir Alafenamide: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir, TAF and/or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirine[a]	↓ Dolutegravir	Use of dolutegravir, emtricitabine and tenofovir alafenamide tablets with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenz[a]	↓ Dolutegravir	If coadministration with efavirenz is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Dosage and Administration (2.4)]*.
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓ Dolutegravir	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Protease inhibitors: Fosamprenavir/ritonavir[a]	↓ Dolutegravir	If coadministration with fosamprenavir/ritonavir is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets
Tipranavir/ritonavir	↓ Dolutegravir	

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, TAF and/or Concomitant Drug	Clinical Comment
	↓ TAF	Coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended because of the TAF component.
Other Agents		
Antiarrhythmics: Dofetilide	↑ Dolutegravir	Coadministration is contraindicated with dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Contraindications (4)]*.
Antimycobacterials: Rifabutin Rifapentine	↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with rifabutin or rifapentine is not recommended.
Rifampin[a]	↓ Dolutegravir ↓ TAF	Coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with rifampin is not recommended because of the TAF component.
Anticonvulsants: Carbamazepine[a]	↓ Dolutegravir ↓ TAF	Consider alternative anticonvulsant. If coadministration with carbamazepine is necessary, an additional 50-mg dose of dolutegravir should be taken, separated by 12 hours from dolutegravir, emtricitabine and tenofovir alafenamide tablets.
Oxcarbazepine Phenytoin Phenobarbital	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Anti-diabetic medications: Metformin[a]	↑ Metformin	Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use with metformin.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ Dolutegravir ↓ TAF	Avoid coadministration with dolutegravir, emtricitabine and tenofovir alafenamide tablets because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacids[a] or laxatives Sucralfate Buffered medications	↓ Dolutegravir	Administer dolutegravir, emtricitabine and tenofovir alafenamide tablets 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or iron[a]	↓ Dolutegravir	When taken with food, dolutegravir, emtricitabine and tenofovir alafenamide tablets and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, dolutegravir, emtricitabine and tenofovir alafenamide tablets should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Potassium channel blockers: Dalfampridine	↑ Dalfampridine	Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking dalfampridine concurrently with dolutegravir, emtricitabine and tenofovir alafenamide tablets should be considered against the risk of seizures in these patients.

[a] See Clinical Pharmacology (12.3) Table 10 or Table 11 for magnitude of interaction.

7.4 Drugs without Clinically Significant Interactions with Dolutegravir, FTC, and TAF

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir *[see Clinical Pharmacology (12.3)]*.

Based on drug interaction studies conducted with the components of emtricitabine and tenofovir alafenamide, no clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following antiretroviral agents: atazanavir with ritonavir or cobicistat, darunavir with ritonavir or cobicistat, dolutegravir, efavirenz, ledipasvir, lopinavir/ritonavir, maraviroc, nevirapine, raltegravir, rilpivirine, and sofosbuvir. No clinically significant drug interactions have been either observed or are expected when emtricitabine and tenofovir alafenamide is combined with the following drugs: buprenorphine, itraconazole, ketoconazole, lorazepam, methadone, midazolam, naloxone, norbuprenorphine, norgestimate/ethinyl estradiol, and sertraline.

7.5 Drugs Affecting Renal Function

Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of dolutegravir, emtricitabine and tenofovir alafenamide tablets with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin) and high-dose or multiple NSAIDs *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from an ongoing birth outcome surveillance study has identified an increased risk of neural tube defects when dolutegravir, a component of dolutegravir, emtricitabine and tenofovir alafenamide tablets, is administered at the time of conception. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk.

Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, of the potential risk of neural tube defects with the use of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Assess the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy or if pregnancy is confirmed in the first trimester. A benefit-risk assessment should consider factors such as feasibility of switching to another antiretroviral regimen, tolerability, ability to maintain viral suppression, and risk of HIV-1 transmission to the infant against the risk of neural tube defects associated with in utero dolutegravir exposure during critical periods of fetal development *[see Warnings and Precautions (5.4)]*.

Available data from the APR show no statistically significant difference in the overall risk of overall major birth defects for emtricitabine (FTC) or tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *(see Data)*. The rate of miscarriage for individual drugs is not reported in the APR.

There are insufficient human data on the use of dolutegravir, emtricitabine and tenofovir alafenamide tablets during pregnancy to definitively assess a drug-associated risk of birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of dolutegravir *[see Data]*. No adverse developmental effects were observed when FTC and TAF were administered separately during the period of organogenesis at exposures 60 and 108 times (mice and rabbits, respectively) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of FTC and TAF *[see Data]*. Likewise, no adverse developmental effects were seen when FTC was administered to mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of FTC. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of TAF.

Data

Human Data:

Dolutegravir

In a birth outcome surveillance study in Botswana, there were 7 cases of neural tube defects reported out of 3,591 deliveries (0.19%) to women who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 11% (21/19,361 deliveries) in the non-dolutegravir arm and 0.07% (87/119,630 deliveries) in the HIV-uninfected arm. Seven cases reported with dolutegravir included 3 cases of myelomeningocele, 2 cases of encephalocele, and one case each of anencephaly and iniencephaly. In the same study, no increased risk of neural tube defects was identified in women who started dolutegravir during pregnancy. Two infants out of 4,448 (0.04%) deliveries to women who started dolutegravir during pregnancy had a neural tube defect, compared with 5 infants out of 6,748 (0.07%) deliveries to women who started non-dolutegravir-containing regimens during pregnancy.

The reported risks of neural tube defects by treatment groups were based on interim analyses from the ongoing surveillance study in Botswana. It is unknown if baseline characteristics were balanced between the study treatment groups. The observed trends of association could change as data accumulate.

Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to definitively address the risk of neural tube defects with dolutegravir.

Data from the birth outcome surveillance study described above and postmarketing sources with more than 1,000 pregnancy outcomes from second and third trimester exposure in pregnant women indicate no evidence of increased risk of adverse birth outcomes.

Based on prospective reports to the APR of 842 exposures to dolutegravir during pregnancy resulting in live births (including 512 exposed in the first trimester), the prevalence of defects in live births was 3.3% (95% CI: 1.9% to 5.3%) following first-trimester exposure to dolutegravir-containing regimens and 4.8% (95% CI: 2.8% to 7.8%) following second-/third-trimester exposure to dolutegravir-containing regimens. In the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP), the background birth defect rate was 2.7%.

Dolutegravir has been shown to cross the placenta. In a clinical trial in Uganda and South Africa in women during the last trimester of pregnancy receiving dolutegravir 50 mg once daily, the ratio of median dolutegravir concentration in fetal umbilical cord to that in maternal peripheral plasma was 1.21 (range 0.51-2.11) (n = 15).

FTC and TAF
Prospective reports from the APR of overall major birth defects in pregnancies exposed to FTC and TAF are compared with a U.S. background major birth defect rate. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

FTC:
Based on prospective reports to the APR of over 5,400 exposures to FTC- containing regimens during pregnancy resulting in live births (including over 3,900 exposed in the first trimester and over 1,500 exposed in the second/third trimester), the prevalence of birth defects in live births was 2.6% (95% CI: 2.2% to 3.2%) and 2.7% (95% CI: 1.9% to 3.7%) following first and second/third trimester exposure, respectively, to FTC-containing regimens.

TAF:
Based on prospective reports to the APR of over 660 exposures to TAF-containing regimens during pregnancy resulting in live births (including over 520 exposed in the first trimester and over 130 exposed in the second/third trimester), the prevalence of birth defects in live births was 4.2% (95% CI: 2.6% to 6.3%) and 3.0% (95% CI: 0.8% to 7.5%) following first and second/third trimester exposure, respectively, to TAF-containing regimens.

Animal Data:
Dolutegravir
Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and also to rats on gestation Day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was

observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

FTC
FTC was administered orally to pregnant mice (250 mg/kg/day, 500 mg/kg/day or 1,000 mg/kg/day) and rabbits (100 mg/kg/day, 300 mg/kg/day or 1,000 mg/kg/day) through organogenesis (on gestation days 6 through 15, and 7 through 19, respectively). No significant toxicological effects were observed in embryo-fetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60 times higher and in rabbits at approximately 108 times higher than human exposures at the recommended daily dose. In a pre/post-natal development study with FTC, mice were administered doses up to 1,000 mg/kg/day; no significant adverse effects directly related to drug were observed in the offspring exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended daily dose.

TAF
TAF was administered orally to pregnant rats (25 mg/kg/day, 100 mg/kg/day or 250 mg/kg/day) and rabbits (10 mg/kg/day, 30 mg/kg/day or 100 mg/kg/day) through organogenesis (on gestation days 6 through 17, and 7 through 20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 53 (rabbits) times higher than the exposure in humans at the recommended daily dose of FTC and tTAF. TAF is rapidly converted to tenofovir; the observed tenofovir exposures in rats and rabbits were 59 (rats) and 93 (rabbits) times higher than human tenofovir exposures at the recommended daily dose. Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to tenofovir disoproxil fumarate (TDF, another prodrug for tenofovir) administration, a pre/post-natal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no adverse effects were observed in the offspring on gestation day 7 (and lactation day 20) at tenofovir exposures of approximately 14 (21) times higher than the exposures in humans at the recommended daily dose of FTC and TAF.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Dolutegravir is present in human milk. It is not known whether dolutegravir affects human milk production or has effects on the breastfed infant. Based on limited data, FTC has been shown to be present in human breast milk; it is not known if TAF is present in human breast milk. Tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF *(see Data).* It is not known if TAF is present in animal milk.

It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets affect milk production or has effects on the breastfed child. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse

reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Data
Animal data:
TAF
Studies in rats and monkeys have demonstrated that tenofovir is secreted in milk. Tenofovir was excreted into the milk of lactating rats following oral administration of TDF (up to 600 mg/kg/day) at up to approximately 24% of the median plasma concentration in the highest dosed animals at lactation day 11. Tenofovir was excreted into the milk of lactating monkeys following a single subcutaneous (30 mg/kg) dose of tenofovir at concentrations up to approximately 4% of plasma concentration, resulting in exposure (AUC) of approximately 20% of plasma exposure.

8.3 Females and Males of Reproductive Potential
In adolescents and adults of childbearing potential currently on dolutegravir, emtricitabine and tenofovir alafenamide tablets who are actively trying to become pregnant or if pregnancy is confirmed in the first trimester, assess the risks and benefits of continuing dolutegravir, emtricitabine and tenofovir alafenamide tablets and discuss with the patient if an alternative treatment should be considered *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Pregnancy Testing
Pregnancy testing is recommended in adolescents and adults of childbearing potential before initiation of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Dosage and Administration (2.1)]*.

Contraception
Adolescents and adults of childbearing potential who are taking dolutegravir, emtricitabine and tenofovir alafenamide tablets should be counseled on the consistent use of effective contraception.

8.4 Pediatric Use
The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets for the treatment of HIV-1 infection in pediatric patients weighing at least 25 kg was established through studies with the individual components *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.2)]*. Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product which cannot be adjusted for pediatric patients weighing less than 25 kg.

The safety and effectiveness of dolutegravir, emtricitabine and tenofovir alafenamide tablets coadministered with an HIV-1 protease inhibitor that is administered with either ritonavir or cobicistat have not been established in pediatric subjects weighing less than 35 kg *[see Dosage and Administration (2.2)]*.

8.5 Geriatric Use

Dolutegravir

Clinical trials of dolutegravir did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of dolutegravir in elderly patients reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12)]*.

FTC and TAF

In clinical trials, 80 of the 97 subjects enrolled aged 65 years and over received FTC + TAF and EVG + COBI. No differences in safety or efficacy have been observed between elderly subjects and adults between 18 and less than 65 years of age.

8.6 Renal Impairment

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination and the dosage of the individual components cannot be adjusted. No dosage adjustment of dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended in patients with mild or moderate renal impairment (estimated creatinine clearance greater than or equal to 30 mL per minute) *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*. There is inadequate information to recommend appropriate dosing of dolutegravir, emtricitabine and tenofovir alafenamide in patients requiring dialysis.

8.7 Hepatic Impairment

No dosage adjustment of dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of dolutegravir, emtricitabine and tenofovir alafenamide has not been studied. Therefore, dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no known specific treatment for overdose with dolutegravir, emtricitabine and tenofovir alafenamide tablets. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required.

Dolutegravir

As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

FTC

Limited clinical experience is available at doses higher than the recommended dose of FTC. In one clinical pharmacology study, single doses of FTC 1,200 mg (6 times the recommended dose

of FTC) were administered to 11 subjects. No severe adverse reactions were reported. The effects of higher doses are not known.

Hemodialysis treatment removes approximately 30% of the FTC dose over a 3-hour dialysis period starting within 1.5 hours of FTC dosing (blood flow rate of 400 mL per minute and a dialysate flow rate of 600 mL per minute). It is not known whether FTC can be removed by peritoneal dialysis.

TAF

Limited clinical experience is available at doses higher than the recommended dose of TAF. A single dose of 125 mg TAF (5 times the TAF dose in 200 mg/25 mg fixed-dose combination emtricitabine and tenofovir alafenamide) was administered to 48 healthy subjects; no serious adverse reactions were reported. The effects of higher doses are unknown. Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

11 DESCRIPTION

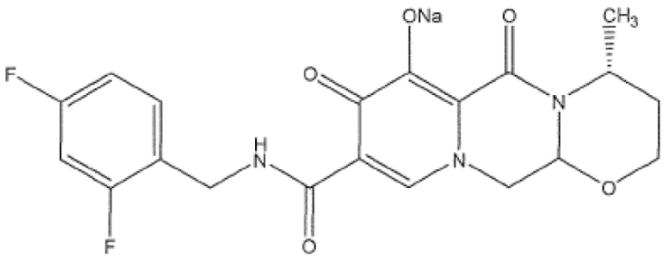
Dolutegravir, emtricitabine and tenofovir alafenamide tablet is a fixed-dose combination product containing dolutegravir (DTG), emtricitabine (FTC) and tenofovir alafenamide (TAF), for oral administration.

- DTG, an HIV integrase strand transfer inhibitor (INSTI).
- FTC, a synthetic nucleoside analog of cytidine, is an HIV nucleoside analog reverse transcriptase inhibitor (HIV NRTI).
- TAF, an HIV NRTI, is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5′-monophosphate.

Each film-coated tablet contains 50 mg of dolutegravir (equivalent to 52.6 of dolutegravir sodium), 200 mg of emtricitabine and 25 mg of tenofovir alafenamide (equivalent to 28.0 mg of tenofovir alafenamide fumarate) and the following inactive ingredients: croscarmellose sodium, lactose monohydrate magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, sodium stearyl fumarate, talc and titanium dioxide.

Dolutegravir

The chemical name of dolutegravir sodium is sodium (4R,12aS)-N-[(2,4-difluorophenyl)methyl]-3,4,6,8,12,12a-hexahydro-7-hydroxy-4-methyl-6,8-dioxo-2H-Pyrido[1’2’:4,5] pyrazino[2,1-b] [1,3]oxazine-9-carboxamide sodium salt . The molecular formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g per mol (as salt). It has the following structural formula:

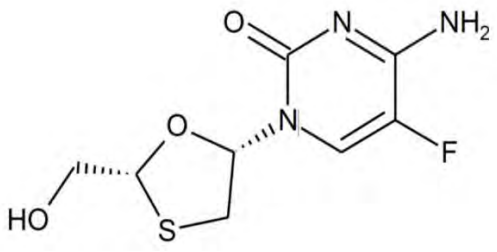


Dolutegravir sodium is a white to light yellow powder and is very slightly soluble in methanol, practically soluble in acetonitrile.

Emtricitabine

The chemical name of FTC is 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone. FTC is the (-)enantiomer of a thio analog of cytidine, which differs from other cytidine analogs in that it has a fluorine in the 5 position.

FTC has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.30 and has the following structural formula:

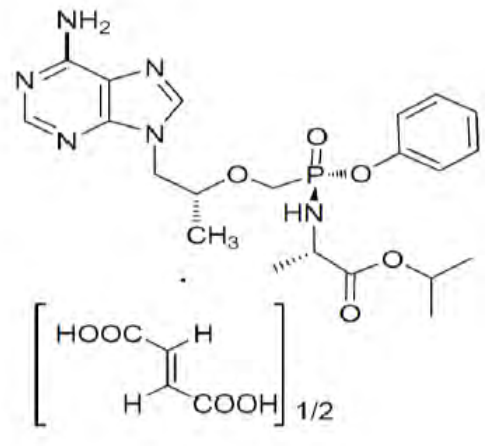


FTC is a white to almost white crystalline powder which is freely soluble in methanol and in water, practically insoluble in dichloromethane.

Tenofovir Alafenamide

The chemical name of tenofovir alafenamide fumarate drug substance is L-alanine,N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methyl ethoxy]methyl]phenoxyphosphinyl]-, 1-methylethyl ester, (2E)-2-butenedioate (2:1).

Tenofovir alafenamide fumarate has a molecular formula of $C_{21}H_{29}O_5N_6P \cdot 1/2(C_4H_4O_4)$ and a molecular weight of 534.5 and has the following structural formula:



Tenofovir alafenamide fumarate is a white to off-white powder or tan powder soluble in methanol and slightly soluble in acetone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination of the HIV-1 antiretroviral drugs dolutegravir, FTC and TAF *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Effects of Dolutegravir on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250 mg suspension (exposures approximately 3-fold of the 50 mg once-daily dose at steady-state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). Dolutegravir did not prolong the QTc interval over 24 hours postdose.

Effects of TAF or FTC on Electrocardiogram

In a thorough QT/QTc study in 48 healthy subjects, TAF at the recommended dose or at a dose approximately 5 times the recommended dose, did not affect the QT/QTc interval and did not prolong the PR interval. The effect of the other component of fixed-dose emtricitabine and tenofovir alafenamide, FTC, or the combination of FTC and TAF on the QT interval is not known.

Effects of Dolutegravir on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13) or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

12.3 Pharmacokinetics

Dolutegravir, Emtricitabine and Tenofovir Alafenamide

The mean systemic exposures dolutegravir, emtricitabine and tenofovir alafenamide from the combination tablets (50 mg/200 mg/25 mg) were comparable to that from TIVICAY® tablets of ViiV Healthcare U.S.A. (containing dolutegravir 50 mg) and DESCOVY® tablets of Gilead Sciences, Inc. U.S.A. (containing emtricitabine 200 mg and tenofovir alafenamide 25 mg), respectively, when single doses were administered to healthy subjects under fasted and fed conditions.

Absorption, Distribution, Metabolism and Excretion:

Dolutegravir

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV-1-infected adult subjects and are provided in Table 5. Exposure to dolutegravir was generally similar between healthy subjects and HIV-1-infected subjects.

Table 5: Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV-1-Infected Adults

Parameter	50 mg Once Daily Geometric Mean (%CV)
$AUC_{(0-24)}$ (mcg•h/mL)	53.6 (27)
C_{max} (mcg/mL)	3.67 (20)
C_{min} (mcg/mL)	1.11 (46)

Following oral administration of dolutegravir, peak plasma concentrations were observed 1 to 3 hours postdose. With once-daily dosing, pharmacokinetic steady-state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max} and C_{24h} ranging from 1.2 to 1.5.

Dolutegravir is a P-gp substrate *in vitro*. The absolute bioavailability of dolutegravir has not been established.

Dolutegravir may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir $AUC_{(0-\infty)}$ by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on *in vivo* data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50 mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.

Cerebrospinal Fluid (CSF):
In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours postdose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.

Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.

In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41). After a single oral dose of [^{14}C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0 % of total dose) and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (less than 1% of the dose).

FTC and TAF

The pharmacokinetic properties of the components of fixed-dose emtricitabine and tenofovir alafenamide are provided in Table 6. The multiple dose pharmacokinetic parameters of FTC and TAF and its metabolite tenofovir are provided in Table 7.

Table 6: Pharmacokinetic Properties of the Components of Fixed-Dose Emtricitabine and Tenofovir Alafenamide

	Emtricitabine	**Tenofovir Alafenamide**
Absorption		
T_{max} (h)	3	1
Effect of high fat meal (relative to fasting)[a]	AUC Ratio = 0.91 (0.89, 0.93) C_{max} Ratio = 0.74 (0.69, 0.78)	AUC Ratio = 1.75 (1.64, 1.88) C_{max} Ratio= 0.85 (0.75, 0.95)
Distribution		
% Bound to human plasma proteins	< 4	~ 80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (> 80% of oral dose)
$t_{1/2}$ (h)c	10	0.51
% Of dose excreted in urine[d]	70	< 1.0
% Of dose excreted in feces[d]	13.7	31.7

PBMCs = peripheral blood mononuclear cells; CES1 = carboxylesterase 1

[a] Values refer to geometric mean ratio [High-fat meal/fasting] in PK parameters and (90% confidence interval). High-calorie/high-fat meal = ~ 800 kcal, 50% fat.

[b] *In vivo*, TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.

[c] $t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, tenofovir diphosphate, has a half-life of 150 to 180 hours within PBMCs.

[d] Dosing in mass balance studies: FTC (single dose administration of [^{14}C] emtricitabine after multiple dosing of emtricitabine for 10 days); TAF (single dose administration of [^{14}C] tenofovir alafenamide).

Table 7: Multiple Dose Pharmacokinetic Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration with Food in HIV-Infected Adults

Parameter Mean (CV%)	Emtricitabine[a]	Tenofovir Alafenamide[b]	Tenofovir[c]
C_{max} (mcg per mL)	2.1 (20.2)	0.16 (51.1)	0.02 (26.1)
AUC_{tau} (mcg•hour per mL)	11.7 (16.6)	0.21 (71.8)	0.29 (27.4)
C_{trough} (mcg per mL)	0.10 (46.7)	NA	0.01 (28.5)

CV = Coefficient of Variation; NA = Not Applicable

[a] From Intensive PK analysis in a phase 2 trial in HIV-infected adults treated with FTC + TAF and EVG + COBI.

[b] From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 539).

[c] From Population PK analysis in two trials of treatment-naïve adults with HIV-1 infection treated with FTC + TAF with EVG + COBI (N = 841).

Effects of Food on Oral Absorption of Dolutegravir, Emtricitabine and Tenofovir Alafenamide:
The pharmacokinetics of dolutegravir, emtricitabine and tenofovir are not affected by food, hence dolutegravir, emtricitabine and tenofovir alafenamide tablets can be administered with or without food.

Specific Populations
Geriatric Patients:
Dolutegravir
Population analyses indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

FTC and TAF
Pharmacokinetics of FTC and TAF have not been fully evaluated in the elderly (65 years of age and older). Population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and Phase 3 trials of FTC + TAF and EVG + COBI showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age *[see Use in Specific Populations (8.5)]*.

Pediatric Patients:
Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product which cannot be adjusted for patients weighing less than 25 kg (55 lbs).

Dolutegravir
The pharmacokinetics of dolutegravir were evaluated in the IMPAACT P1093 trial and in 2 weight-band-based pharmacokinetic substudies from the ODYSSEY trial. Mean dolutegravir $AUC_{0\text{-}24h}$ and C_{24h} in HIV-1-infected pediatric subjects were comparable to those in adults after 50 mg once daily or 50 mg twice daily.

FTC and TAF

Exposures of FTC and TAF achieved in 23 pediatric subjects between the ages of 6 to less than 12 years and weighing at least 25 kg (55 lbs) who received FTC+TAF with EVG+COBI were higher (20% to 80% for AUC) than exposures achieved in adults following the administration of this dosage regimen; however, the increase was not considered clinically significant (Table 8).

Table 8: Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 6 to less than 12 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	3.4 (27.0)	0.31 (61.2)	0.03 (20.8)
AUC_{tau} (microgram•hour per mL)	20.6[b] (18.9)	0.33 (44.8)	0.44 (20.9)
C_{trough} (microgram per mL)	0.11 (24.1)	NA	0.02 (24.9)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in virologically-suppressed pediatric subjects with HIV-1 infection (N=23).

Mean exposures of TAF in 24 pediatric subjects aged 12 to less than 18 years who received FTC+TAF with EVG+COBI were decreased (23% for AUC) and FTC exposures were similar compared to exposures achieved in treatment-naïve adults following administration of this dosage regimen. The TAF exposure differences are not thought to be clinically significant based on exposure-response relationships (Table 9).

Table 9: Multiple Dose PK Parameters of Emtricitabine, Tenofovir Alafenamide, and its Metabolite Tenofovir Following Oral Administration of FTC+TAF with EVG+COBI in HIV-Infected Pediatric Subjects Aged 12 to less than 18 Years[a]

Parameter Mean (CV%)	Emtricitabine	Tenofovir Alafenamide	Tenofovir
C_{max} (microgram per mL)	2.3 (22.5)	0.17 (64.4)	0.02 (23.7)
AUC_{tau} (microgram•hour per mL)	14.4 (23.9)	0.20[b] (50.0)	0.29[b] (18.8)
C_{trough} (microgram per mL)	0.10[b] (38.9)	NA	0.01 (21.4)

CV = Coefficient of Variation; NA = Not Applicable

a. From Intensive PK analysis in a trial in treatment-naïve pediatric subjects with HIV-1 infection (N=24).

b. N=23

Gender and Race:

Dolutegravir

Population analyses using pooled pharmacokinetic data from adult trials indicated gender or race had no clinically relevant effect on the exposure of dolutegravir.

FTC and TAF
Based on population pharmacokinetic analyses, there are no clinically meaningful differences based on race or gender.

Patients with Renal Impairment:
Dolutegravir, emtricitabine and tenofovir alafenamide tablets are not recommended for patients with severe renal impairment (estimated creatinine clearance below 30 mL per min) because dolutegravir, emtricitabine and tenofovir alafenamide tablets is a fixed-dose combination product and the dosage of the individual components cannot be adjusted *[see Dosage and Administration (2.3)]*.

Patients with Hepatic Impairment:
Dolutegravir
Dolutegravir is primarily metabolized and eliminated by the liver. In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Class B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of dolutegravir has not been studied.

FTC
The pharmacokinetics of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of hepatic impairment should be limited.

TAF
Clinically relevant changes in tenofovir pharmacokinetics in subjects with hepatic impairment were not observed in subjects with mild to moderate (Child-Pugh Class A and B) hepatic impairment.

Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV) Co-infection:
FTC and TAF
The pharmacokinetics of FTC and TAF have not been fully evaluated in subjects infected with hepatitis B and/or C virus.

Dolutegravir
Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Drug Interaction Studies:
The drug interaction trials described were conducted with dolutegravir, emtricitabine, and/or tenofovir alafenamide as single entities; no drug interaction trials have been conducted using the fixed-dose combination of dolutegravir, emtricitabine and tenofovir alafenamide.

Dolutegravir

The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 10 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 11.

Dosing or regimen recommendations as a result of established and other potentially significant drug-drug interactions with dolutegravir are provided in Table 4 *[see Drug Interactions (7.3)]*.

Table 10: Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	**Dose of Dolutegravir,**	**n**	**Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00**		
			C_{max}	**AUC**	**C_{τ} or C_{24}**
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15[a]	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformin 500 mg twice daily	50 mg twice daily	15[a]	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	–	0.95 (0.79 to 1.15)	–
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

[a]The number of subjects represents the maximum number of subjects that were evaluated.

Table 11: Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300 mg/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.5 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600 mg/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600 mg/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400 mg/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400 mg/100 mg twice daily	30 mg once daily	15	1 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500 mg/200 mg twice daily	50 mg once daily	14	0.54 (0.5 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX®) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.7 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.5 to 0.81)	0.61 (0.47 to 0.8)	0.61 (0.47 to 0.8)

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16[c]	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day®) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.
[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.
[c] The number of subjects represents the maximum number of subjects that were evaluated.

FTC and TAF

The effects of coadministered drugs on the exposure of TAF are shown in Table 12 and the effects of emtricitabine and tenofovir alafenamide or the components on the exposure of coadministered drugs are shown in Table 13 [these studies were conducted with fixed-dose emtricitabine and tenofovir alafenamide or the components of fixed-dose emtricitabine and tenofovir alafenamide (FTC or TAF) administered alone]. For information regarding clinical recommendations, *see Drug Interactions (7).*

Table 12: Drug Interactions: Changes in TAF Pharmacokinetic Parameters in the Presence of Coadministered Drug(s)[a]

Coadministered Drug	Coadministered Drug(s) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of TAF PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 (+ 100 ritonavir)	10	10	1.77 (1.28, 2.44)	1.91 (1.55, 2.35)	NC
Cobicistat	150	8	12	2.83 (2.20, 3.65)	2.65 (2.29, 3.07)	NC
Darunavir	800 (+ 150 cobicistat)	25[b]	11	0.93 (0.72, 1.21)	0.98 (0.80, 1.19)	NC
Darunavir	800 (+ 100 ritonavir)	10	10	1.42 (0.96, 2.09)	1.06 (0.84, 1.35)	NC
Dolutegravir	50	10	10	1.24 (0.88, 1.74)	1.19 (0.96, 1.48)	NC
Efavirenz	600	40[b]	11	0.78 (0.58,1.05)	0.86 (0.72, 1.02)	NC
Lopinavir	800 (+ 200 ritonavir)	10	10	2.19 (1.72, 2.79)	1.47 (1.17, 1.85)	NC
Rilpivirine	25	25	17	1.01 (0.84, 1.22)	1.01 (0.94, 1.09)	NC
Sertraline	50 (dosed as a single dose)	10[c]	19	1.00 (0.86, 1.16)	0.96 (0.89,1.03)	NC

NC = Not Calculated

[a] All interaction studies conducted in healthy volunteers.

[b] Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF).

[c] Study conducted with FTC + TAF with EVG + COBI.

Table 13: Drug Interactions: Changes in PK Parameters for Coadministered Drug in the Presence of Fixed-Dose Emtricitabine and Tenofovir Alafenamide or the Individual Components[a]

Coadministered Drug	Coadministered Drug(s) Dosage (once daily) (mg)	Tenofovir Alafenamide Dosage (once daily) (mg)	N	Mean Ratio of Coadministered Drug PK Parameters (90% CI); No effect = 1.00		
				C_{max}	AUC	C_{min}
Atazanavir	300 + 100 ritonavir	10	10	0.98 (0.89, 1.07)	0.99 (0.96, 1.01)	1.00 (0.96, 1.04)
Darunavir	800 + 150 cobicistat	25[b]	11	1.02 (0.96, 1.09)	0.99 (0.92, 1.07)	0.97 (0.82, 1.15)
Darunavir	800 + 100 ritonavir	10	10	0.99 (0.91, 1.08)	1.01 (0.96, 1.06)	1.13 (0.95, 1.34)
Dolutegravir	50 mg	10	10	1.15 (1.04, 1.27)	1.02 (0.97, 1.08)	1.05 (0.97, 1.13)
Lopinavir	800 + 200 ritonavir	10	10	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)	0.98 (0.85, 1.12)
Midazolam[c]	2.5 (single dose, orally)	25	18	1.02 (0.92, 1.13)	1.13 (1.04, 1.23)	NC
	1 (single dose, intravenous)			0.99 (0.89, 1.11)	1.08 (1.04, 1.14)	NC
Rilpivirine	25	25	16	0.93 (0.87, 0.99)	1.01 (0.96, 1.06)	1.13 (1.04, 1.23)
Sertraline	50 (dosed as a single dose)	10[d]	19	1.14 (0.94, 1.38)	0.93 (0.77, 1.13)	NC

NC = Not Calculated

[a] All interaction studies conducted in healthy volunteers.

[b] Study conducted with emtricitabine and tenofovir alafenamide (FTC/TAF).

[c] A sensitive CYP3A4 substrate.

[d] Study conducted with FTC + TAF with EVG + COBI.

12.4 Microbiology

Mechanism of Action

Dolutegravir:

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC_{50} values of 2.7 nM and 12.6 nM.

FTC:

FTC, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA polymerases α, β, Ɛ and mitochondrial DNA polymerase γ.

***TAF*:**
TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analog). Plasma exposure to TAF allows for permeation into cells and then TAF is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Tenofovir has activity against HIV-1. Cell culture studies have shown that both tenofovir and FTC can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of toxicity to mitochondria in cell culture.

Antiviral Activity in Cell Culture
Dolutegravir:
Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC_{50} values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC_{50} values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

FTC:
The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in T lymphoblastoid cell lines, the MAGI-CCR5 cell line, and primary peripheral blood mononuclear cells. The EC_{50} values for FTC were in the range of 1.3 to 640 nM. FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 7 to 75 nM) and showed strain specific activity against HIV-2 (EC_{50} values ranged from 7 to 1,500 nM).

In a study of FTC with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand transfer inhibitors [INSTIs] and PIs) no antagonism was observed for these combinations.

TAF:
The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells and CD4-T lymphocytes. The EC_{50} values for TAF ranged from 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

Antiviral Activity in Combination with Other Antiviral Agents

Dolutegravir:

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; nonnucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the NRTIs, abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide. Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir or inhibited by the antiviral, ribavirin.

TAF:

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs and PIs) no antagonism was observed for these combinations.

Resistance

Cell Culture:

Dolutegravir

Dolutegravir-resistant viruses were selected in cell culture starting from different wild-type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

FTC

HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in subjects treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

TAF

HIV-1 isolates with reduced susceptibility to TAF were selected in cell culture. HIV-1 isolates selected by TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT was observed.

In Clinical Trials

Dolutegravir:

No subject who received dolutegravir 50-mg once-daily in the treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment-emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a

corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials.

In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI-resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

FTC and TAF:
The resistance profile of FTC and TAF in combination with other antiretroviral agents for the treatment of HIV-1 infection is based on studies of FTC+TAF with EVG+COBI in the treatment of HIV-1 infection. In a pooled analysis of antiretroviral-naïve subjects, genotyping was performed on plasma HIV-1 isolates from all subjects with HIV-1 RNA greater than 400 copies per mL at confirmed virologic failure, at Week 48, or at time of early study drug discontinuation. Genotypic resistance developed in 7 of 14 evaluable subjects. The resistance- associated substitutions that emerged were M184V/I (N=7) and K65R (N=1). Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase.

One subject was identified with emergent resistance to FTC or TAF (M184M/I) out of 4 virologic failure subjects in a clinical study of virologically-suppressed subjects who switched from a regimen containing FTC+TDF to FTC+TAF with EVG+COBI (N=799).

Cross-Resistance
Dolutegravir:
Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.

Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains
Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI- resistant HIV-1 mutant clones compared with the wild-type strain.

FTC:
FTC-resistant viruses with the M184V or I substitution were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine.

Viruses harboring substitutions conferring reduced susceptibility to stavudine and zidovudine-thymidine analog substitutions (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution or other substitutions associated with resistance to NNRTIs was susceptible to FTC.

TAF:
Tenofovir resistance substitutions K65R and K70E result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine and tenofovir.

HIV-1 with multiple thymidine analog substitutions (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N/R) or multinucleoside resistant HIV-1 with a T69S double insertion mutation or with a Q151M substitution complex including K65R, showed reduced susceptibility to TAF in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Dolutegravir:
Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug-related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at a dose of 50 mg twice daily.

Mutagenesis
Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Impairment of Fertility
In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at a dose of 50 mg twice daily.

FTC:
In long-term carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice at doses up to 750 mg per kg per day (23 times the human systemic exposure at the recommended dose of 200 mg per day in dolutegravir, emtricitabine and tenofovir alafenamide tablets) or in rats at doses up to 600 mg per kg per day (28 times the human systemic exposure at the recommended dose in dolutegravir, emtricitabine and tenofovir alafenamide tablets).

FTC was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or mouse micronucleus assays.

FTC did not affect fertility in male rats at approximately 140 times or in male and female mice at approximately 60 times higher exposures (AUC) than in humans given the recommended 200 mg daily dosage in dolutegravir, emtricitabine and tenofovir alafenamide tablets. Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily exposures (AUC) of approximately 60 times higher than human exposures at the recommended 200 mg daily dosage in dolutegravir, emtricitabine and tenofovir alafenamide tablets.

TAF:
Since TAF is rapidly converted to tenofovir and a lower tenofovir exposure in rats and mice was observed after TAF administration compared to TDF administration, carcinogenicity studies were conducted only with TDF. Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the recommended dose of TDF (300 mg) for HIV-1 infection. The tenofovir exposure in these studies was approximately 167 times (mice) and 55 times (rat) those observed in humans after administration of the daily recommended dose of dolutegravir, emtricitabine and tenofovir alafenamide tablets. At the high dose in female mice, liver adenomas were increased at tenofovir exposures approximately 10 times (300 mg TDF) and 167 times (dolutegravir, emtricitabine and tenofovir alafenamide tablets) the exposure observed in humans. In rats, the study was negative for carcinogenic findings.

TAF was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

There were no effects on fertility, mating performance or early embryonic development when TAF was administered to male rats at a dose equivalent to 62 times (25 mg TAF) the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 14 days prior to mating through Day 7 of gestation.

13.2 Animal Toxicology and/or Pharmacology
TAF
Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three- and nine- month administration of TAF; reversibility was seen after a three- month recovery period. No eye toxicity was observed in the dog at systemic exposures of 5 (TAF) and 15 (tenofovir) times the exposure seen in humans with the recommended daily TAF dose in dolutegravir, emtricitabine and tenofovir alafenamide tablets.

14 CLINICAL STUDIES

14.1 Adult Subjects

Dolutegravir

Treatment-Naïve Subjects:

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir DF [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11 % had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm^3, and 39% received fixed-dose abacavir sulfate and lamivudine (EPZICOM); these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) are found in Table 14. There was no treatment-emergent resistance to dolutegravir or to the NRTI background.

Table 14: Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96

	SPRING-2 Week 96	
	Dolutegravir 50 mg Once Daily + 2NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**
HIV-1 RNA < 50 copies/mL	82%	78%
Treatment difference[a]	4.9% (95% CI: -0.6%, 10.3%)[d]	
Virologic nonresponse	5%	10%
Data in window not < 50 copies/mL	1%	3%
Discontinued for lack of efficacy	2%	3%
Discontinued for other reasons while not suppressed	< 1%	3%
Change in ART regimen	< 1%	< 1%
No virologic data	12%	12%
Reasons		
Discontinued study/study drug due to adverse event or death[b]	2%	2%
Discontinued study/study drug for other reasons[c]	8%	9%
Missing data during window but on study	2%	< 1%
Proportion (%) of Subjects with HIV-1 RNA < 50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤100,000	84%	83%
>100,000	79%	63%
Gender		
Male	84%	79%
Female	70%	68%
Race		
White	83%	78%
African-American/African Heritage/Other	77%	75%

NRTI = nucleoside reverse transcriptase inhibitor

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.
[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.
[d] The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving dolutegravir and 86% in the raltegravir group, with a treatment difference of 2.6% and 95% CI of (-1.9%, 7.2%).
[e] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

In SPRING-2, virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of fixed-dose abacavir sulfate and lamivudine (EPZICOM) or fixed-dose emtricitabine/tenofovir DF (TRUVADA) as NRTI background regimen. The median change in CD4+ cell counts from baseline was 276 cells per mm^3 in the group receiving dolutegravir and 264 cells per mm^3 for the raltegravir group at 96 weeks.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects:
In SAILING, there were 715 subjects included in the efficacy and safety analyses (see full prescribing information for dolutegravir). At Week 48, 71% of subjects randomized to dolutegravir plus background regimen versus 64% of subjects randomized to raltegravir plus background regimen had HIV-1 RNA less than 50 copies per mL (treatment difference and 95% CI: 7.4% [0.7%, 14.2%]).

FTC and TAF
In trials of FTC+TAF with EVG+COBI in HIV-1 infected adults as initial therapy in those with no antiretroviral treatment history (N=866) and to replace a stable antiretroviral regimen in those who were virologically-suppressed for at least 6 months with no known resistance substitutions (N=799), 92% and 96% of patients in the two populations, respectively, had HIV-1 RNA less than 50 copies per mL at Week 48.

In a trial in 248 HIV-1 infected adults with estimated creatinine clearance greater than 30 mL per minute but less than 70 mL per minute, 95% (235/248) of the combined population of treatment-naïve subjects (N=6) began on FTC+TAF with EVG+COBI and those previously virologically-suppressed on other regimens (N=242) and switched to FTC+TAF with EVG+COBI had HIV-1 RNA less than 50 copies per mL at Week 24.

14.2 Pediatric Subjects

Dolutegravir
Dolutegravir, in combination with other antiretroviral drugs was evaluated in treatment-experienced, INSTI-naïve, HIV-1-infected subjects aged 6 to less than 18 years in a 48-week open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 (NCT01302847). Subjects aged 12 to less than 18 years were enrolled in Cohort 1 and subjects aged 6 to less than 12 years were enrolled in Cohort 2A. At 48 weeks, 61% (14/23) of subjects aged 12 to less than 18 years treated with dolutegravir once daily plus optimized background therapy achieved virologic response defined as HIV-1 RNA less than 50 copies per mL. Across both cohorts, virologic suppression at Week 48 was achieved in 67% (16/24) of subjects weighing at least 40 kg.

FTC and TAF

An open-label, single arm trial of FTC+TAF with EVG+COBI enrolled 50 treatment-naïve HIV-1 infected adolescents aged 12 to less than 18 years weighing at least 35 kg (cohort 1) and 52 virologically suppressed children aged 6 to less than 12 years weighing at least 25 kg (cohort 2). In cohort 1, the virologic response rate (i.e., HIV-1 RNA less than 50 copies per mL) was 92% (46/50) and the mean increase from baseline in CD4+ cell count was 224 cells per mm^3 at Week 48. In cohort 2, 98% (51/52) of subjects remained virologically suppressed at Week 48. From a mean (SD) baseline CD4+ cell count of 961 (275.5) cells per mm^3, the mean change from baseline in CD4+ cell count was -66 cells per mm^3 and the mean (SD) change in CD4% was -0.6% (4.4%) at Week 48. All subjects maintained CD4+ cell counts above 400 cells/mm^3 *[see Adverse Reactions (6.1)]*.

In a separate open-label single arm trial of FTC+TAF with bictegravir that enrolled 24 virologically-suppressed children at least 2 years of age and weighing at least 14 to less than 25 kg (cohort 3), 91% (20/22) of subjects remained virologically suppressed at Week 24. From a mean (SD) baseline CD4+ count of 1104 (440), the mean (SD) change from baseline in CD4+ cell count was −126 (264) cells per mm^3, and the mean (SD) change in CD4% was 0.2% (4.4%) at Week 24.

16 HOW SUPPLIED/STORAGE AND HANDLING

Dolutegravir, emtricitabine and tenofovir alafenamide tablets are white to off-white colored, modified capsule shaped, film-coated tablets, debossed with “L6” on one side and “L” on other side and supplied as follows:

Bottle of 30 tablets with desiccant and child-resistant cap (NDC 70748-184-06)
Bottle of 60 tablets with desiccant and child-resistant cap (NDC 70748-184-07)
Bottle of 90 tablets with desiccant and child-resistant cap (NDC 70748-184-09)

Store below 30ºC (86ºF). Store and dispense in the original bottle, protect it from moisture, and keep bottle tightly closed. Do not remove desiccant. Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Post-Treatment Acute Exacerbation of Hepatitis B in Patients with HBV Infection

Inform patients that severe acute exacerbations of hepatitis B have been reported in patients who are infected with HBV and have discontinued products containing FTC and/or TDF, and may likewise occur with discontinuation of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Warnings and Precautions (5.1)]*. Advise HBV-infected patients to not discontinue dolutegravir, emtricitabine and tenofovir alafenamide tablets without first informing their healthcare provider.

Drug Interactions

Dolutegravir, emtricitabine and tenofovir alafenamide tablets may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or

nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.4), Drug Interactions (7)]*.

Hypersensitivity Reactions
Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets and other suspect agents and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea-colored urine, pale-colored stools or bowel movements, nausea, vomiting, loss of appetite or pain, aching or sensitivity on the right side below the ribs) *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity
Inform patients that hepatotoxicity has been reported with dolutegravir, one component of dolutegravir, emtricitabine and tenofovir alafenamide tablets *[see Warnings and Precautions (5.3)]*. Advise patients that laboratory monitoring for hepatoxicity during therapy with dolutegravir, emtricitabine and tenofovir alafenamide tablets is recommended, especially for patients with liver disease, such as hepatitis B or C.

Embryo-Fetal Toxicity
Advise adolescents and adults of childbearing potential, including those actively trying to become pregnant, to discuss the risks and benefits of dolutegravir, emtricitabine and tenofovir alafenamide tablets with their healthcare provider to determine if an alternative treatment should be considered at the time of conception through the first trimester of pregnancy. If pregnancy is confirmed in the first trimester, advise patients to contact their healthcare provider *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Adolescents and adults of childbearing potential taking dolutegravir, emtricitabine and tenofovir alafenamide tablets should be counseled on the consistent use of effective contraception *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Immune Reconstitution Syndrome
Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.6)]*.

New Onset or Worsening Renal Impairment
Advise patients to avoid taking dolutegravir, emtricitabine and tenofovir alafenamide tablets with concurrent or recent use of nephrotoxic agents. Postmarketing cases of renal impairment, including acute renal failure, have been reported *[see Warnings and Precautions (5.7)]*.

Lactic Acidosis and Severe Hepatomegaly
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of drugs similar to dolutegravir, emtricitabine and tenofovir alafenamide tablets. Treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets should be suspended in patients who develop clinical symptoms suggestive of lactic acidosis or pronounced hepatotoxicity *[see Warnings and Precautions (5.8)]*.

Lactation
Instruct mothers with HIV-1 infection not to breastfeed because of the risk of passing the HIV-1 virus to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dosage
Instruct patients that if they miss a dose of dolutegravir, emtricitabine and tenofovir alafenamide tablets, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose.

Storage
Instruct patients to store dolutegravir, emtricitabine and tenofovir alafenamide tablets in the original package, protect from moisture and keep the bottle tightly closed. Do not remove desiccant.

Manufactured by:
Lupin Limited
Nagpur – 441108
INDIA

Revised: January 2023

Patient Information
Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets,
50 mg/200 mg/25 mg

What is dolutegravir, emtricitabine and tenofovir alafenamide tablets?

Dolutegravir, emtricitabine and tenofovir alafenamide tablets is a prescription medicine that is used as a complete regimen to treat human immunodeficiency virus (HIV-1) infection in adults and children who weigh at least 25 kg (55 pounds).

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

Dolutegravir, emtricitabine and tenofovir alafenamide tablets contain 3 prescription medicines dolutegravir, emtricitabine and tenofovir alafenamide.

It is not known if dolutegravir, emtricitabine and tenofovir alafenamide tablets for treatment of HIV-1 infection is safe and effective in children who weigh less than 25 kg (55 pounds).

Do not take dolutegravir, emtricitabine and tenofovir alafenamide tablets if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir, emtricitabine, or tenofovir alafenamide
- take dofetilide

Before taking dolutegravir, emtricitabine and tenofovir alafenamide tablets, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had liver problems, including hepatitis B or C infection
- have kidney problems
- are pregnant or plan to become pregnant. Dolutegravir, one of the medicines in dolutegravir, emtricitabine and tenofovir alafenamide tablets, may harm your unborn baby.
  - Your healthcare provider may prescribe a different medicine than dolutegravir, emtricitabine and tenofovir alafenamide tablets if you are planning to become pregnant or if pregnancy is confirmed during the first 12 weeks of pregnancy.
  - If you can become pregnant, your healthcare provider may perform a pregnancy test before you start treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets.
  - If you can become pregnant, you and your healthcare provider should talk about the use of effective birth control (contraception) during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets.
  - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take dolutegravir, emtricitabine and tenofovir alafenamide tablets**
  - You should not breastfeed if you have HIV-1 because the risk of passing HIV-1 to your baby.
  - At least two of the medicines in dolutegravir, emtricitabine and tenofovir alafenamide tablets (dolutegravir and emtricitabine) pass into your breast milk. It is not known if the other medicine in dolutegravir, emtricitabine and tenofovir alafenamide tablets can pass into your breast milk.
  - Talk with your healthcare provider about the best way to feed your baby during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Some medicines may interact with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- **Do not start a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take dolutegravir, emtricitabine and tenofovir alafenamide tablets with other medicines.

How should I take dolutegravir, emtricitabine and tenofovir alafenamide tablets?

- **Take dolutegravir, emtricitabine and tenofovir alafenamide tablets exactly as your healthcare provider tell you.**
- Take dolutegravir, emtricitabine and tenofovir alafenamide tablets with or without food.

- Do not change your dose or stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets without first talking with your healthcare provider. Stay under a healthcare provider's care when taking dolutegravir, emtricitabine and tenofovir alafenamide tablets. Do not miss a dose of dolutegravir, emtricitabine and tenofovir alafenamide tablets.
- If you miss a dose of dolutegravir, emtricitabine and tenofovir alafenamide tablets, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, dolutegravir, emtricitabine and tenofovir alafenamide tablets should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets:
  - If you take dolutegravir, emtricitabine and tenofovir alafenamide tablets with food, you may take these supplements at the same time that you take dolutegravir, emtricitabine and tenofovir alafenamide tablets.
  - If you do not take dolutegravir, emtricitabine and tenofovir alafenamide tablets with food, take dolutegravir, emtricitabine and tenofovir alafenamide tablets at least 2 hours before or 6 hours after you take these supplements.
- Do not run out of dolutegravir, emtricitabine and tenofovir alafenamide tablets. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much dolutegravir, emtricitabine and tenofovir alafenamide tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of dolutegravir, emtricitabine and tenofovir alafenamide tablets?

- **Dolutegravir, emtricitabine and tenofovir alafenamide tablets can cause serious side effects, including:**
- **Allergic reactions. Call your healthcare provider right away if you develop a rash with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets and get medical help right away if you develop a rash with any of the following signs or symptoms:**
  - fever
  - generally ill feeling
  - tiredness
  - muscle or joint aches
  - blisters or sores in mouth
  - blisters or peeling of the skin
  - redness or swelling of the eyes
  - swelling of the mouth, face, lips, or tongue
  - problems breathing
- **Liver problems.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets. Liver problems, including liver failure, have also happened in people without a history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver.

  Tell your healthcare provider right away if you develop any of the following signs or symptoms of liver problems:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - nausea or vomiting
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach area

- **Worsening of hepatitis B virus (HBV) infection. Your healthcare provider will test you for HBV infection before or when you start treatment with dolutegravir, emtricitabine and tenofovir alafenamide tablets. If you have HBV infection and take dolutegravir, emtricitabine and tenofovir alafenamide tablets, your HBV may get worse (flare-up) if you stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets. A "flare-up" is when your HBV infection suddenly returns in a worse way than before.**
  - Do not run out of dolutegravir, emtricitabine and tenofovir alafenamide tablets. Refill your prescription or talk to your healthcare provider before your dolutegravir, emtricitabine and tenofovir alafenamide tablets is all gone.
  - Do not stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets without first talking to your healthcare provider.

- If you stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets, your healthcare provider will need to check your health often and do blood tests regularly for several months to check your liver, and may give you a medicine to treat hepatitis B. Tell your healthcare provider about any new or unusual symptoms you may have after you stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets.

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking medicines to treat HIV-1 infection. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having any new symptoms after starting your HIV-1 medicine.
- **New or worse kidney problems, including kidney failure.** Your healthcare provider should do blood and urine tests to check your kidneys before you start and while taking dolutegravir, emtricitabine and tenofovir alafenamide tablets. Your healthcare provider may tell you to stop taking dolutegravir, emtricitabine and tenofovir alafenamide tablets if you develop new or worse kidney problems.
- **Too much lactic acid in your blood (lactic acidosis).** Too much lactic acid is a serious but rare medical emergency that can lead to death. Tell your healthcare provider right away if you get these symptoms: weakness or being more tired than usual, unusual muscle pain, being short of breath or fast breathing, stomach pain with nausea and vomiting, cold or blue hands and feet, feel dizzy or lightheaded, or a fast or abnormal heartbeat.
- **Severe liver problems.** In rare cases, severe liver problems can happen that can lead to death. Tell your healthcare provider right away if you get these symptoms: skin or the white part of your eyes turns yellow, dark "tea-colored" urine, light-colored stools, loss of appetite for several days or longer, nausea, or stomach-area pain.

The most common side effects of dolutegravir, emtricitabine and tenofovir alafenamide tablets include:

- trouble sleeping
- nausea
- tiredness
- headache
- diarrhea

These are not all of the possible side effects of dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store dolutegravir, emtricitabine and tenofovir alafenamide tablets?

- Store dolutegravir, emtricitabine and tenofovir alafenamide tablets below 30°C (86°F).
- Keep and dispense dolutegravir, emtricitabine and tenofovir alafenamide tablets in its original container.
- Keep the container tightly closed.
- The bottle of dolutegravir, emtricitabine and tenofovir alafenamide tablets contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

Keep dolutegravir, emtricitabine and tenofovir alafenamide tablets and all medicines out of reach of children.

General information about the safe and effective use of dolutegravir, emtricitabine and tenofovir alafenamide tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use dolutegravir, emtricitabine and tenofovir alafenamide tablets for a condition for which it was not prescribed. Do not give dolutegravir, emtricitabine and tenofovir alafenamide tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about dolutegravir, emtricitabine and tenofovir alafenamide tablets that is written for health professionals. For more information, go to www.lupinpharmaceuticals.com or call 1-800-399-2561.

What are the ingredients in dolutegravir, emtricitabine and tenofovir alafenamide tablets?

Active ingredients: dolutegravir, emtricitabine and tenofovir alafenamide.

Inactive ingredients: croscarmellose sodium, lactose monohydrate magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, sodium stearyl fumarate, talc and titanium dioxide.

Manufactured by:
Lupin Limited
Nagpur – 441108
INDIA
Code No. MH/DRUGS/25-ND/59

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 01/2023

NDC 70748-184-06

Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets

50 mg / 200 mg / 25 mg

Note to pharmacist: Do not cover ALERT box with pharmacy label

ALERT: Find out about medicine that should NOT be taken with Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets.

Rx only

LUPIN

30 Tablets

Each film-coated tablet contains 50 mg of dolutegravir (equivalent to 52.6 mg of dolutegravir sodium), 200 mg of emtricitabine and 25 mg of tenofovir alafenamide (equivalent to 28.0 mg of tenofovir alafenamide fumarate).
Usual Dosage: See prescribing information for dosage information.
KEEP OUT OF THE REACH OF CHILDREN.
Storage: Store below 30°C (86°F).
Store and dispense in the original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant. This bottle is child-resistant.

This Product has been manufactured under a license from Gilead Sciences, Inc., Medicines Patent Pool and ViiV Healthcare.
Any other use is not authorized.

Manufactured by:
Lupin Limited
Nagpur – 441108 INDIA

Code No. MH/DRUGS/25-ND/59

XXXXXX

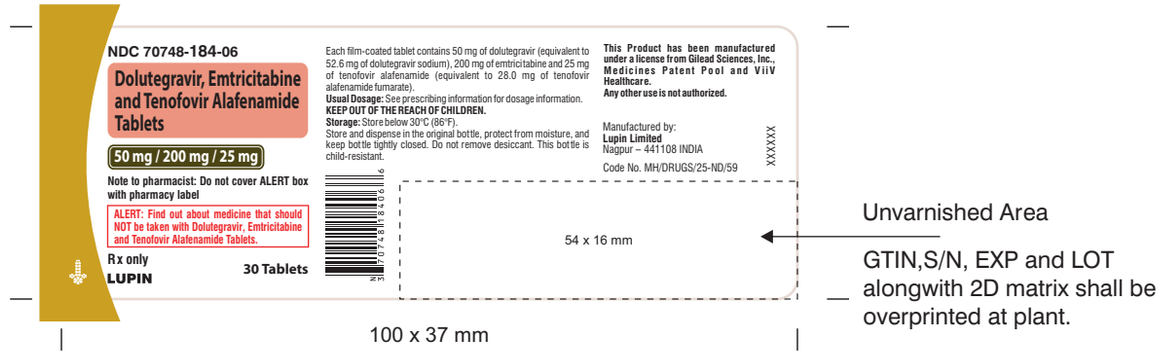
54 x 16 mm

Unvarnished Area

GTIN,S/N, EXP and LOT alongwith 2D matrix shall be overprinted at plant.

175% enlarged

Unwinding Direction



Unvarnished Area

GTIN,S/N, EXP and LOT alongwith 2D matrix shall be overprinted at plant.

Customer Name :	US	**Location :**	Nagpur
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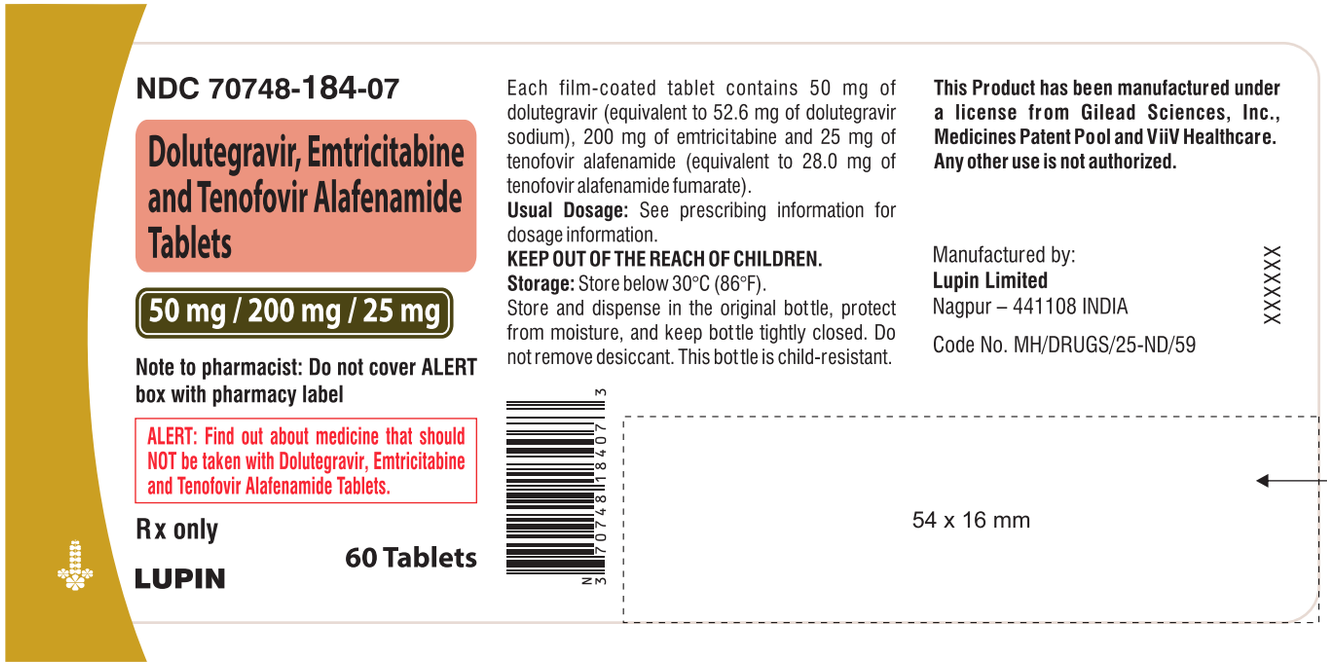
Dimensions :	100 x 37 mm	**Barcode Type (Ex. NDC, PZN, EAN-13) :**	UPC(A)
Substrate with GSM :	----	**Pharmacode value :**	NA
Varnish Type :	----	**Component :**	Label
Pantone Colours :	PANTONE 7753 C, PANTONE 486 C, PANTONE 5815 C, Black Text, PANTONE 1788 C, Dieline - Does not print, Area for Batch Coding		
Reason for Change:	New Artwork		
Unicorn Creation D/Lupin/Regulatory/US/Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets/			



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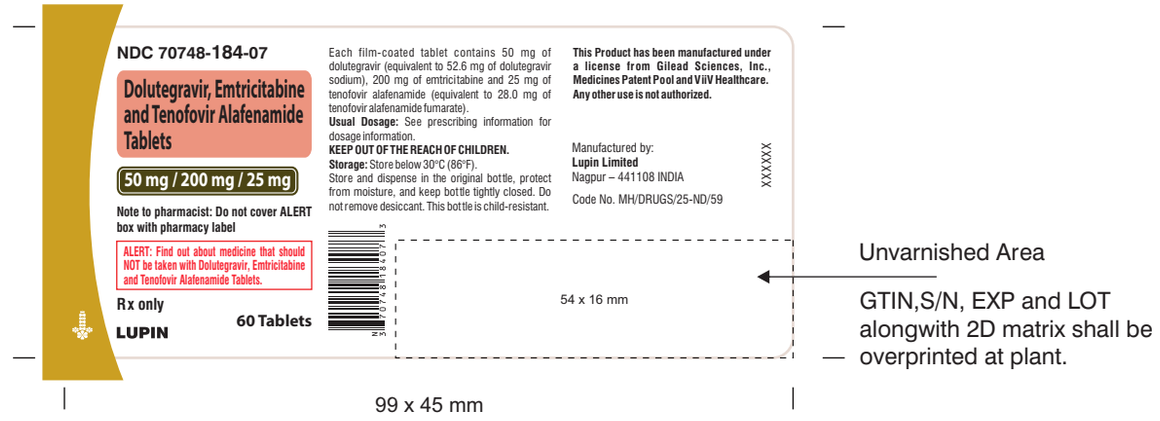
Unwinding Direction



99 x 45 mm

Customer Name :	US	**Location :**	Nagpur
Prepared On :	13/01/2023	**Tracking No. :**	10
Product name :	Dolutegravir, Emtricitabine and Tenofovir Alafenamide 60's Tablets Label		
Material code :	XXXXXX	**Supercedes Material code :**	NA
Minimum Font Size :	4.5 pt	**Barcode value :**	370748184073
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Varnish Type :	----	**Component :**	Label
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Reason for Change:	New Artwork		
Unicorn Creation D/Lupin/Regulatory/US/Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets/			

Reference ID: 5112360

Unwinding Direction

Customer Name :	US	**Location :**	Nagpur
Prepared On :	13/01/2023	**Tracking No. :**	11
Product name :	Dolutegravir, Emtricitabine and Tenofovir Alafenamide 90's Tablets Label		
Material code :	XXXXXX	**Supercedes Material code :**	NA
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Dimensions :	99 x 45 mm	**Barcode Type (Ex. NDC, PZN, EAN-13) :**	UPC(A)
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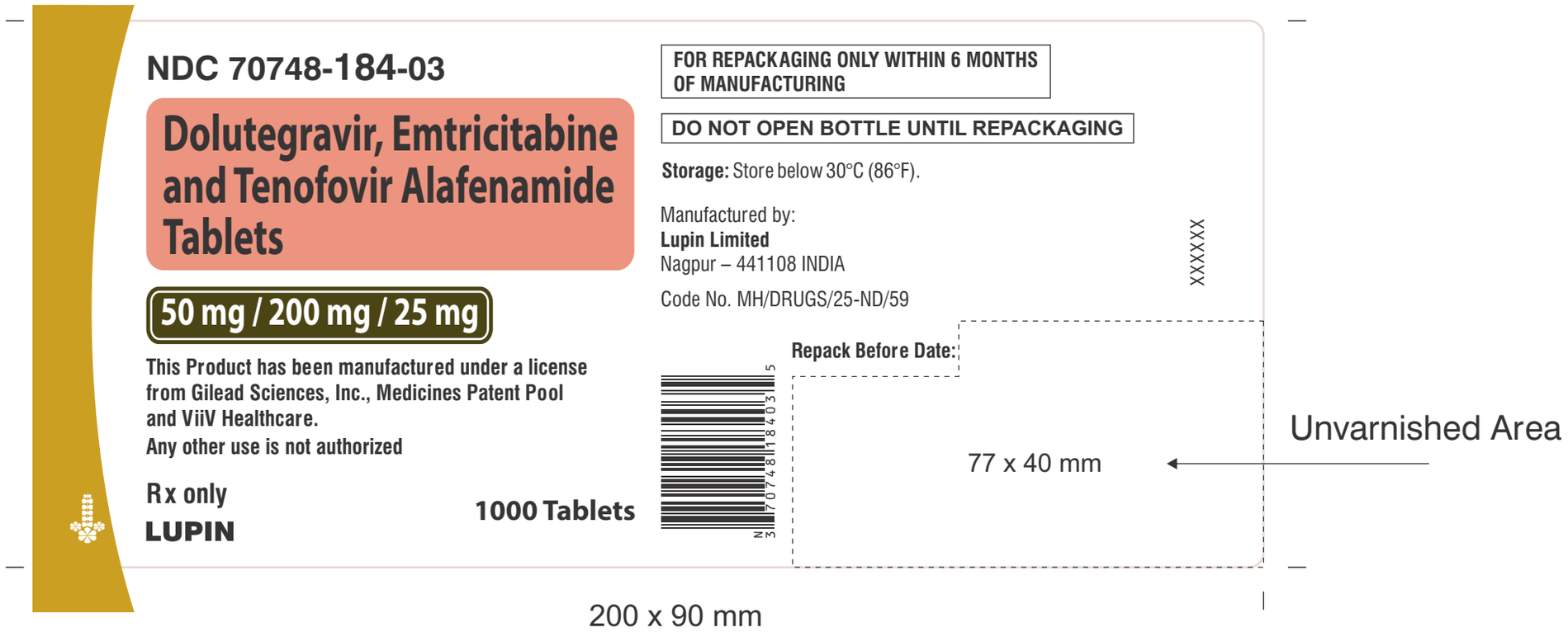
Pantone Colours :	PANTONE 7753 C, PANTONE 486 C, PANTONE 5815 C, Black Text, PANTONE 1788 C, Dieline - Does not print, Area for Batch Coding		
Reason for Change:	New Artwork		
Unicorn Creation D/Lupin/Regulatory/US/Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets/			

Reference ID: 5112360

Unwinding Direction



Customer Name :	US	**Location :**	Nagpur
Prepared On :	29/04/2021	**Tracking No. :**	04
Product name :	Dolutegravir, Emtricitabine and Tenofovir Alafenamide 1000's Tablets Label		
Material code :	XXXXXX	**Supercedes Material code :**	NA
Minimum Font Size :	8.5 pt	**Barcode value :**	370748184035
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Varnish Type :	----	**Component :**	Label
Pantone Colours :	PANTONE 7753 C; PANTONE 486 C; PANTONE 5815 C; Black Text; Dieline - Does not print; Area for Batch Coding		
Reason for Change:	New Artwork		
Unicorn Creation D/Lupin/Regulatory/US/Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets/			

Reference ID: 5112360

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SARITA D BOYD
01/19/2023 04:34:59 PM

Versiune de imprimare
Salvare

Recipisa

Respondent
Codul fiscal: 1003600113573, denumire: LISMEDFARM S.R.L.
A prezentat raportul: RSF1_21
Pentru perioada fiscala: A/2023
Data prezentarii: 14.05.2024
Marca temporală a raportului înregistrat în Sistemul de Raportare Electronică și expediat pentru procesare în Sistemul Informațional al BNS : 14.05.2024 10:08:46

Versiune de imprimare
Salvare

Recipisa 2

Respondent
Codul fiscal: 1003600113573, denumire: LISMEDFARM S.R.L.
A prezentat raportul: RSF1_21
Pentru perioada fiscala: A/2023
Data prezentarii: 14.05.2024
Marca temporală a raportului înregistrat în Sistemul Informațional al BNS : 16.05.2024 10:54:00

Biroul Național de Statistică (BNS) a recepționat varianta electronică a raportului, expediat de DVs. Urmează verificarea și validarea raportului de către specialistul BNS pe domeniu.

Data prezentării 14.05.2024 10:08:46

Anexe la SNC
"Prezentarea situatiilor financiare"
Aprobat de Ministerul Finantelor
al Republicii Moldova

SITUAŢIILE FINANCIARE

pentru perioada 01.01.2023 - 31.12.2023

Entitatea: LISMEDFARM S.R.L.
Cod CUIÎO: 38183026
Cod IDNO: 1003600113573

Sediul:
MD: 2002
Raionul(municipiul): 103, DDF BOTANICA
Cod CUATM: 0110, SEC.BOTANICA
Strada: sos. Muncesti, 167/B, mun. Chisinau

Activitatea principală: G4646, Comert cu ridicata al produselor farmaceutice
Forma de proprietate: 15, Proprietatea privată
Forma organizatorico-juridică: 530, Societăți cu răspundere limitată

Date de contact:
Telefon: 022804799
WEB:
E-mail: contabil@lismedfarm.md
Numele și coordonatele al contabilului-șef: Dl (dna) Alii Veronica Tel.

Numărul mediu al salariaților în perioada de gestiune: 23 **persoane.**

Persoanele responsabile de semnarea situațiilor financiare* Chitic Ecaterina

Unitatea de măsură: leu

BILANŢUL

Anexa 1

la 31.12.2023

Nr. cpt.	Indicatori	Cod rd.	Sold la	
			Începutul perioadei de gestiune	Sfîrşitul perioadei de gestiune
1	2	3	4	5
	A C T I V			
A.	**ACTIVE IMOBILIZATE** **I. Imobilizări necorporale**			
	1. Imobilizări necorporale în curs de execuție	010	0	0
	2. Imobilizări necorporale în exploatare, total	020	11906	12503
	din care: 2.1. concesiuni, licențe și mărci	021	0	0
	2.2. drepturi de autor și titluri de protecție	022	0	0
	2.3. programe informatice	023	11906	12503

2.4. alte imobilizări necorporale	024	0	0
3. Fond comercial	030	0	0
4. Avansuri acordate pentru imobilizări necorporale	040	0	0
Total imobilizări necorporale (rd.010 + rd.020 + rd.030 + rd.040)	050	11906	12503
II. Imobilizări corporale			
1. Imobilizări corporale în curs de execuție	060	0	0
2. Terenuri	070	233698	233698
3. Mijloace fixe, total	080	8841484	8281249
din care: 3.1. clădiri	081	7716121	7425976
3.2. construcții speciale	082	270381	142218
3.3. mașini, utilaje și instalații tehnice	083	198435	171970
3.4. mijloace de transport	084	614026	497069
3.5. inventar și mobilier	085	10503	5757
3.6. alte mijloace fixe	086	32018	38259
4. Resurse minerale	090	0	0
5. Active biologice imobilizate	100	0	0
6. Investiții imobiliare	110	0	0
7. Avansuri acordate pentru imobilizări corporale	120	0	0
Total imobilizări corporale (rd.060 + rd.070 + rd.080 + rd.090 + rd.100 + rd.110 + rd.120)	130	9075182	8514947
III. Investiții financiare pe termen lung			
1. Investiții financiare pe termen lung în părți neafiliate	140	0	0
2. Investiții financiare pe termen lung în părți afiliate, total	150	0	0
din care: 2.1. acțiuni și cote de participație deținute în părțile afiliate	151	0	0
2.2 împrumuturi acordate părților afiliate	152	0	0
2.3 împrumuturi acordate aferente intereselor de participare	153	0	0
2.4 alte investiții financiare	154	0	0
Total investiții financiare pe termen lung (rd.140 + rd.150)	160	0	0
IV. Creanțe pe termen lung și alte active imobilizate			
1. Creanțe comerciale pe termen lung	170	0	0
2. Creanțe ale părților afiliate pe termen lung	180	0	0
inclusiv: creanțe aferente intereselor de participare	181	0	0
3. Alte creanțe pe termen lung	190	0	0

	4. Cheltuieli anticipate pe termen lung	200	0	0
	5. Alte active imobilizate	210	0	0
	Total creanțe pe termen lung și alte active imobilizate (rd.170 + rd.180 + rd.190 + rd.200 + rd.210)	220	0	0
	TOTAL ACTIVE IMOBILIZATE (rd.050 + rd.130 + rd.160 + rd.220)	230	9087088	8527450
B.	**ACTIVE CIRCULANTE** **I. Stocuri**			
	1. Materiale și obiecte de mică valoare și scurtă durată	240	25806	16440
	2. Active biologice circulante	250	0	0
	3. Producția în curs de execuție	260	0	0
	4. Produse și mărfuri	270	19326489	19273484
	5. Avansuri acordate pentru stocuri	280	5040292	5411036
	Total stocuri (rd.240 + rd.250 + rd.260 + rd.270 + rd.280)	290	24392587	24700960
	II. Creanțe curente și alte active circulante			
	1. Creanțe comerciale curente	300	15129505	8162767
	2. Creanțe ale părților afiliate curente	310	0	0
	inclusiv: creanțe aferente intereselor de participare	311	0	0
	3. Creanțe ale bugetului	320	3461127	4105302
	4. Creanțele ale personalului	330	31000	35582
	5. Alte creanțe curente	340	33345	268035
	6. Cheltuieli anticipate curente	350	14153	8132
	7. Alte active circulante	360	0	0
	Total creanțe curente și alte active circulante (rd.300 + rd.310 + rd.320 + rd.330 + rd.340 + rd.350 + rd.360)	370	18669130	12579818
	III. Investiții financiare curente			
	1. Investiții financiare curente în părți neafiliate	380	0	0
	2. Investiții financiare curente în părți afiliate, total	390	0	0
	din care: 2.1. acțiuni și cote de participație deținute în părțile afiliate	391	0	0
	2.2. împrumuturi acordate părților afiliate	392	0	0
	2.3. împrumuturi acordate aferente intereselor de participare	393	0	0
	2.4. alte investiții financiare în părți afiliate	394	0	0
	Total investiții financiare curente (rd.380 + rd.390)	400	0	0
	IV. Numerar și documente bănești	410	1975580	4939169
	TOTAL ACTIVE CIRCULANTE (rd.290 + rd.370 + rd.400 + rd.410)	420	45037297	42219947

	TOTAL ACTIVE (rd.230 + rd.420)	430	54124385	50747397
	P A S I V			
C.	**CAPITAL PROPRIU** **I. Capital social și neînregistrat**			
	1. Capital social	440	918181	918181
	2. Capital nevărsat	450	(0)	(0)
	3. Capital neînregistrat	460	0	0
	4. Capital retras	470	(0)	(0)
	5. Patrimoniul primit de la stat cu drept de proprietate	480	0	0
	Total capital social și neînregistrat (rd.440 + rd.450 + rd.460 + rd.470 + rd.480)	490	918181	918181
	II. Prime de capital	500	0	0
	III. Rezerve			
	1. Capital de rezervă	510	0	0
	2. Rezerve statutare	520	4050	4050
	3. Alte rezerve	530	0	0
	Total rezerve (rd.510 + rd.520 + rd.530)	540	4050	4050
	IV. Profit (pierdere)			
	1. Corecții ale rezultatelor anilor precedenți	550	X	0
	2. Profit nerepartizat (pierdere neacoperită) al anilor precedenți	560	35800350	35800350
	3. Profit net (pierdere netă) al perioadei de gestiune	570	X	7948680
	4. Profit utilizat al perioadei de gestiune	580	X	(0)
	Total profit (pierdere) (rd.550 + rd.560 + rd.570 + rd.580)	590	35800350	43749030
	V. Rezerve din reevaluare	600	0	0
	VI. Alte elemente de capital propriu	610	0	0
	TOTAL CAPITAL PROPRIU (rd.490 + rd.500 + rd.540 + rd.590 + rd.600 + rd.610)	620	36722581	44671261
D.	**DATORII PE TERMEN LUNG**			
	1. Credite bancare pe termen lung	630	0	0
	2. Împrumuturi pe termen lung	640	8026112	0
	din care: 2.1. împrumuturi din emisiunea de obligațiuni	641	0	0
	inclusiv: împrumuturi din emisiunea de obligațiuni convertibile	642	0	0

	2.2. alte împrumuturi pe termen lung	643	8026112	0
	3. Datorii comerciale pe termen lung	650	0	0
	4. Datorii față de părțile afiliate pe termen lung	660	0	0
	inclusiv: datorii aferente intereselor de participare	661	0	0
	5. Avansuri primite pe termen lung	670	0	0
	6. Venituri anticipate pe termen lung	680	0	0
	7. Alte datorii pe termen lung	690	0	0
	TOTAL DATORII PE TERMEN LUNG (rd.630 + rd.640 + rd.650 + rd.660 + rd.670 + rd.680 + rd.690)	700	8026112	0
E.	**DATORII CURENTE**			
	1. Credite bancare pe termen scurt	710	0	0
	2. Împrumuturi pe termen scurt, total	720	0	195000
	din care: 2.1. împrumuturi din emisiunea de obligațiuni	721	0	0
	inclusiv: împrumuturi din emisiunea de obligațiuni convertibile	722	0	0
	2.2. alte împrumuturi pe termen scurt	723	0	195000
	3. Datorii comerciale curente	730	8938350	5467214
	4. Datorii față de părțile afiliate curente	740	0	0
	inclusiv: datorii aferente intereselor de participare	741	0	0
	5. Avansuri primite curente	750	72026	41705
	6. Datorii față de personal	760	0	0
	7. Datorii privind asigurările sociale și medicale	770	72075	65727
	8. Datorii față de buget	780	43974	39618
	9. Datorii față de proprietari	790	0	0
	10. Venituri anticipate curente	800	0	0
	11. Alte datorii curente	810	249267	266872
	TOTAL DATORII CURENTE (rd.710 + rd.720 + rd.730 + rd.740 + rd.750 + rd.760 + rd.770 + rd.780 + rd.790 + rd.800 + rd.810)	820	9375692	6076136
F.	**PROVIZIOANE**			
	1. Provizioane pentru beneficiile angajaților	830	0	0
	2. Provizioane pentru garanții acordate cumpărătorilor/clienților	840	0	0
	3. Provizioane pentru impozite	850	0	0
	4. Alte provizioane	860	0	0
	TOTAL PROVIZIOANE (rd.830 + rd.840 + rd.850 + rd.860)	870	0	0
	TOTAL PASIVE (rd.620 + rd.700 + rd.820 + rd.870)	880	54124385	50747397

SITUAŢIA DE PROFIT ŞI PIERDERE

de la 01.01.2023 pînă la 31.12.2023

Anexa 2

Indicatori	Cod rd.	Perioada de gestiune	
		precedenta	curenta
1	2	3	4
Venituri din vînzări, total	010	95300233	94511274
din care: venituri din vînzarea produselor și mărfurilor	011	95299733	94510774
venituri din prestarea serviciilor și executarea lucrărilor	012	500	500
venituri din contracte de construcție	013	0	0
venituri din contracte de leasing	014	0	0
venituri din contracte de microfinanţare	015	0	0
alte venituri din vînzări	016	0	0
Costul vînzărilor, total	020	84519235	83418200
din care: valoarea contabilă a produselor și mărfurilor vîndute	021	84519235	83418200
costul serviciilor prestate și lucrărilor executate terților	022	0	0
costuri aferente contractelor de construcție	023	0	0
costuri aferente contractelor de leasing	024	0	0
costuri aferente contractelor de microfinanţare	025	0	0
alte costuri aferente vînzărilor	026	0	0
Profit brut (pierdere brută) (rd.010 - rd.020)	030	10780998	11093074
Alte venituri din activitatea operațională	040	8316357	6145998
Cheltuieli de distribuire	050	4965557	5501258
Cheltuieli administrative	060	1259190	1811450
Alte cheltuieli din activitatea operațională	070	192839	413353
Rezultatul din activitatea operațională: profit (pierdere) (rd.030 + rd.040 - rd.050 - rd.060 - rd.070)	080	12679769	9513011
Venituri financiare, total	090	2138571	1650996
din care: venituri din interese de participare	091	0	0
inclusiv: veniturile obținute de la părțile afiliate	092	0	0
venituri din dobînzi	093	1830	0
inclusiv: veniturile obținute de la părțile afiliate	094	0	0
venituri din alte investiții financiare pe termen lung	095	12028	0
inclusiv: veniturile obținute de la părțile afiliate	096	0	0
venituri aferente ajustărilor de valoare privind investițiile financiare pe termen lung și curente	097	0	0
venituri din ieșirea investițiilor financiare	098	0	0

venituri aferente diferențelor de curs valutar și de sumă	099	2124713	1650996
Cheltuieli financiare, total	100	2070177	2097377
din care: cheltuieli privind dobînzile	101	0	0
inclusiv: cheltuielile aferente părților afiliate	102	0	0
cheltuieli aferente ajustărilor de valoare privind investițiile financiare pe termen lung și curente	103	0	0
cheltuieli aferente ieșirii investițiilor financiare	104	0	0
cheltuieli aferente diferențelor de curs valutar și de sumă	105	1905887	2097377
Rezultatul: profit (pierdere) financiar(ă) (rd.090 - rd.100)	110	68394	-446381
Venituri cu active imobilizate și excepționale	120	5310	16635
Cheltuieli cu active imobilizate și excepționale	130	0	9135
Rezultatul din operațiuni cu active imobilizate și excepționale: profit (pierdere) (rd.120 - rd.130)	140	5310	7500
Rezultatul din alte activități: profit (pierdere) (rd.110 + rd.140)	150	73704	-438881
Profit (pierdere) pînă la impozitare (rd.080 + rd.150)	160	12753473	9074130
Cheltuieli privind impozitul pe venit	170	1565939	1125450
Profit net (pierdere netă) al perioadei de gestiune (rd.160 - rd.170)	180	11187534	7948680

SITUAŢIA MODIFICĂRILOR CAPITALULUI PROPRIU

de la 01.01.2023 pînă la 31.12.2023

Anexa 3

Nr. d/o	Indicatori	Cod rd	Sold la începutul perioadei de gestiune	Majorări	Diminuări	Sold la sfîrşitul perioadei de gestiune
1	2	3	4	5	6	7
I.	**Capital social și neînregistrat**					
	1. Capital social	010	918181	0	0	918181
	2. Capital nevărsat	020	(0)	(0)	(0)	(0)
	3. Capital neînregistrat	030	0	0	0	0
	4. Capital retras	040	(0)	(0)	(0)	(0)
	5. Patrimoniul primit de la stat cu drept de proprietate	050	0	0	0	0
	Total capital social și neînregistrat (rd.010 + rd.020 + rd.030 + rd.040 + rd.050)	060	918181	0	0	918181
II.	**Prime de capital**	070	0	0	0	0

III.	**Rezerve**					
	1. Capital de rezervă	080	0	0	0	0
	2. Rezerve statutare	090	4050	0	0	4050
	3. Alte rezerve	100	0	0	0	0
	Total rezerve (rd.080 + rd.090 + rd.100)	110	4050	0	0	4050
IV.	**Profit (pierdere)**					
	1. Corecții ale rezultatelor anilor precedenți	120	X	0	0	0
	2. Profit nerepartizat (pierdere neacoperită) al anilor precedenți	130	35800350	0	0	35800350
	3. Profit net (pierdere netă) al perioadei de gestiune	140	X	7948680	0	7948680
	4. Profit utilizat al perioadei de gestiune	150	X	(0)	(0)	(0)
	Total profit (pierdere) (rd.120 + rd.130 + rd.140 + rd.150)	160	35800350	7948680	0	43749030
V.	**Rezerve din reevaluare**	170	0	0	0	0
VI.	**Alte elemente de capital propriu**	180	0	0	0	0
	Total capital propriu (rd.060 + rd.070 + rd.110 + rd.160 + rd.170 + rd.180)	190	36722581	7948680	0	44671261

SITUAŢIA FLUXURILOR DE NUMERAR

de la 01.01.2023 pînă la 31.12.2023

Anexa 4

Indicatori	Cod rd	Perioada de gestiune	
		precedentă	curentă
1	2	3	4
Fluxuri de numerar din activitatea operațională			
Încasări din vînzări	010	66148952	68770563
Plăți pentru stocuri și servicii procurate	020	69150464	55643548
Plăți către angajați și organe de asigurare socială și medicală	030	2343801	2837398
Dobînzi plătite	040	0	0
Plata impozitului pe venit	050	1172166	1529028
Alte încasări	060	4428799	4374981
Alte plăți	070	3008563	10063332
Fluxul net de numerar din activitatea operațională (rd.010 - rd.020 - rd.030 - rd.040 - rd.050 + rd.060 - rd.070)	080	-5097243	3072238
Fluxuri de numerar din activitatea de investiții			
Încasări din vînzarea activelor imobilizate	090	0	0
Plăți aferente intrărilor de active imobilizate	100	0	0

Dobînzi încasate	110	1830	0
Dividende încasate	120	0	0
inclusiv: dividende încasate din străinătate	121	0	0
Alte încasări (plăți)	130	0	0
Fluxul net de numerar din activitatea de investiții (rd.090 - rd.100 + rd.110 + rd.120 ± rd.130)	140	1830	0
Fluxuri de numerar din activitatea financiară			
Încasări sub formă de credite și împrumuturi	150	399000	1575432
Plăți aferente rambursării creditelor și împrumuturilor	160	430000	1385014
Dividende plătite	170	1730709	0
inclusiv: dividende plătite nerezidenților	171	0	0
Încasări din operațiuni de capital	180	0	0
Alte încasări (plăți)	190	1796	0
Fluxul net de numerar din activitatea financiară (rd.150 - rd.160 - rd.170 + rd.180 ± rd.190)	200	-1759913	190418
Fluxul net de numerar total (± rd.080 ± rd.140 ± rd.200)	210	-6855326	3262656
Diferențe de curs valutar favorabile (nefavorabile)	220	351213	-299067
Sold de numerar la începutul perioadei de gestiune	230	8479693	1975580
Sold de numerar la sfîrşitul perioadei de gestiune (± rd.210 ± rd.220 + rd.230)	240	1975580	4939169

Documente atașate - Notă explicativă (fișierul pdf)

Nota explicativa la RSF1 LISMEDFARM no com.signed.signed.pdf

la Documentația standard din
Ordinul Ministrului Finanțelor
nr. 115 din 15 septembrie 2021

Specificaţii de preţ

[Acest tabel va fi completat de către ofertant în coloanele 5,6,7,8 şi 11 la necesitate, iar de către autoritatea contractantă – în coloanele 1,2,3,4,9,10]

Numărul procedurii de achiziție: ocds-b3wdp1-MD-1732642177049 din 12.12.2024

Obiectul de achiziției:"Achiziţionarea medicamentelor pentru realizarea Programului Național de prevenire și control HIV/SIDA și ITS pentru anul 2025 (repetat nr. 1)"

	Cod CPV	Denumirea bunurilor/serviciilor	Unitatea de măsură	Cantitatea	Preţ unitar (fără TVA)	Preţ unitar (cu TVA)	Suma fără TVA	Suma cu TVA	Termenul de livrare/prestare	Clasificație bugetară (IBAN)	Discount%
	1	2	3	4	5	6	7	8	9	10	11
Nr. lot		**Bunuri**									
5	33600000-6	Dolutegravirum+Emtricitabinum+Tenofovirium alafenamidum 50 mg+200 mg+25 mg	Comprimat	1028609	3.13	3.3804	3219546.17	3477109.864	Tranșe de livrare: I tranșă – 100 % Martie 2025.	Conform SIA RSAP Mtender	0
		TOTAL					**3219546.17**	**3477109.864**			

Semnat:_____ Numele, Prenumele: Vlad Chitic În calitate de: Director executiv

Ofertantul: Lismedfarm S.R.L. Adresa: 167/B, sos. Muncesti, MD-2002 Chisinau, Republica Moldova

Anexa nr. 22
la Documentația standard din
Ordinul Ministrului Finanțelor
nr. 115 din 15 septembrie 2021

Specificaţii tehnice

[Acest tabel va fi completat de către ofertant în coloanele 2, 3, 4, 6, 7, iar de către autoritatea contractantă – în coloanele 1, 5.]

Numărul procedurii de achiziție: ocds-b3wdp1-MD-1732642177049 din 12.12.2024

Obiectul achiziției: **"Achiziționarea medicamentelor pentru realizarea Programului Național de prevenire și control HIV/SIDA și ITS pentru anul 2025 (repetat nr. 1)"**

	Denumirea bunurilor/serviciilor	**Denumirea modelului bunului/ serviciului**	**Țara de origine**	**Producătorul**	**Specificarea tehnică deplină solicitată de către autoritatea contractantă**	**Specificarea tehnică deplină propusă de către ofertant**	**Standarde de referință**
	1	2	3	4	5	6	7
Nr. Lot	**Bunuri**						
5	Dolutegravirum+Emtricitabinum+ Tenofovirium alafenamidum 50 mg+200 mg+25 mg	Dolutegravir, Emtricitabine and Tenofovir Alafenamide Tablets, 50 mg/200 mg/25 mg	India	Lupin Ltd.	ATC J05AR. Forma farmaceutica Comprimate. Mod de administrare per os. Unitatea de măsură: comprimat. Se acceptă: 1.medicamente autorizate în Republica Moldova (la momentul deschiderii ofertelor) sau 2.medicamente autorizate (la momentul deschiderii ofertelor) în cadrul Comisiei medicamentului din cadrul Agenției Medicamentului și Dispozitivelor Medicale (AMDM), incluse în Registrul produselor medicamentoase avizate pozitiv în rezultatul expertizei și testării de către Laboratorul de Control al Calității Medicamentelor (conform informației publicate pe pagina oficială a AMDM) sau 3. medicamente neautorizate în Republica Moldova (la momentul deschiderii ofertelor). I. În cazul ofertării medicamentelor neautorizate în Republica Moldova (la momentul deschiderii ofertelor), se va prezenta: 1) dovada deținerii Certificatului de bună practică de fabricație a medicamentului (GMP), eliberat conform recomandărilor Agenției Europene a Medicamentului (EMA), OMS sau a Biroului Federal de control asupra calității alimentelor și medicamentelor (FDA), copii autentificate (cu aplicarea suplimentară a semnăturii electronice a participantului), conform prevederilor cadrului normativ- valabil la momentul deschiderii ofertelor; 2) Se va prezenta dovada că medicamentele ofertate se regăsesc în lista medicamentelor precalificate (https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products). Prioritate vor avea medicamentele care se regăsesc în această listă. În cazul în care nici un medicament ofertat nu se regăsește în lista medicamentelor precalificate, se vor evalua ofertele la care s-a prezentat dovada autorizării medicamentului ofertat de către FDA (SUA) sau EMA, sau una din autoritățile naționale competente în domeniul medicamentului din țările membre ale Spațiului Economic European, sau de către Autoritățile Sigure de Reglementare în domeniul medicamentului, membre ale Consiliului Internațional pentru armonizarea cerințelor tehnice pentru medicamentele de uz uman (ICH) sau în țara de origine. II. Se va asigura prezența în ambalajul secundar al produsului a prospectului/rezumatul caracteristicii produsului în limba de stat, sau în limba de stat și în limba rusă.	ATC J05AR. Forma farmaceutica Comprimate. Mod de administrare per os. Unitatea de măsură: comprimat. Prezența în ambalajul secundar al produsului a prospectului/rezumatul caracteristicii produsului în limba de stat. Tranșe de livrare: I tranșă – 100 % Martie 2025. Facturare - N90	Precalificat, GMP

Semnat:_____ Numele, Prenumele: Vlad Chitic În calitate de: Director executiv

Ofertantul: Lismedfarm S.R.L. Adresa: 167/B, sos. Muncesti, MD-2002 Chisinau, Republica Moldova

LISMEDFARM S.R.L.
Șos. Munceşti, 167/B, MD – 2002, mun. Chișinău, Republica Moldova
tel.: 022-80-47-98, 022-55-64-38, 022-56-94-91, e-mail: oficiu@lismedfarm.md,
web: https://lismedfarm.md, c/f: 1003600113573, TVA: 0304618, director – Ecaterina Chitic

PROCURĂ nr. 18 din 03.11.2023

Subsemnata, Chitic Ecaterina, în calitate de fondator unic şi administrator al S.R.L. „Lismedfarm", IDNO **1003600113573**, cu sediul în Republica Moldova, mun. Chișinău, șos. Munceşti, 167/B, MD-2002, împuternicească pe d-nul **Chitic Vlad**, directorul executiv al companiei S.R.L. „Lismedfarm", cetățeanul al Republicii Moldova, având IDNP **2007042030196**, posesor al buletinului de identitate seria **B** nr. **01232897** eliberat la data de **23.10.2023**, pentru a reprezenta interesele companiei S.R.L. „Lismedfarm". în faţa tuturor persoanelor competente, inclusiv in fata instanţelor de judecată, organelor de stat / autorităţilor publice (de toate nivelurile), instituţii (asociaţii, uniuni, etc.) publice, bancare, instituţii obştești, şi/sau profesionale, persoanele fizice şi/sau juridice în orice procedură judiciară, civilă, penală, administrativă sau contravenţionala.

D-ul Chitic Vlad se autorizează pentru orice act de administrare şi dispoziţie pentru buna desfăşurare a activităţii S.R.L. „Lismedfarm".

Pentru utilizarea scopului menționat, mandatarului i se oferă:

- dreptul de a îndeplini din numele companiei toate actele procedurale inclusiv va prezenta la orice bancă şi va putea efectua orice operaţiuni financiar-bancare pe conturile deschise pe numele S.R.L .„Lismedfarm", necesare desfăşurării activităţii societăţii, inclusiv deschideri, derijerii şi lichidări conturilor, va perfecta şi va inainta cereri şi declaraţi necesare, va prezenta documentaţia solicitată, va efectua plăţi, încasări, viramente, depuneri etc. din şi în aceste conturi, va achita orice taxe, va ridica extrasele de cont, îndeplinind toate formalităţile necesare, cu dreptul de a semna din numele companiei, în limita prezentului mandat;
- este împuternicit cu toate drepturile procesual penale și procesual civile, inclusiv de a achita taxa de stat și a înainta cererea prealabilă/somația; a semna și depune acțiunea, cererea introductiva, cererea de admitere a creanței, cerere de validare a popririi, referința, cererea de apel, cererea de recurs, cererea de revizuire; a recurge la arbitraj; a renunța total/parțial la pretențiile din acțiune; a majora/reduce cuantumul pretențiilor din acțiune; a prezenta probe; a modifica temeiul sau obiectul acțiunii; a recunoaște acțiunea; a recurge și participa la mediere, a negocia și semna tranzacții de împăcare; a intenta acțiunea reconvențională; a transmite împuternicirile unei alte persoane; a ataca hotărîrea judecătorească cu apel, recurs sau revizuire și a-i schimba modul de executare; a reclama probe; a da explicații și a pleda în dezbaterile judiciare; a strămuta pricina;; a depune cereri și plîngeri în adresa organelor abilitate, inclusiv privind intentarea cauzei penale; a solicita si primi informatii/acte de la organele de stat și persoane; a depune cereri de intervenție în proces;
- dreptul de a duce tratativele şi de a încheia contracte cu persoane fizice sau juridice, în vederea desfăşurării activităţii societăţii şi a unei bune administrări a acesteia, fiind nelimitat de suma tranzacției, va putea achiziționa în numele societăţii documentația de evidența contabilă-financiară de strictă evidență (chitanţiere şi facturi fiscale şi alte) și alte acte cu sau fără regim special, de a depune toate raporturile financiare /bilanţurile şi de a supraveghea şi verifica evidenţa contabilă a societăţii, cu dreptul de a perfecta, semna și inainta orice contestaţii şi plângeri la actele organelor financiare, fiscale sau a altor organe de control, cu dreptul de a semna procese verbale de constatare, declaraţii fiscale, declaraţii unice, facturi fiscale va obţine semnături electronice în numele societăţii, fiind direct răspunzător pentru acţiunile sale proprie;
- de a duce tratativele, încheia şi semna în numele societăţii şi pentru aceasta contracte de prestări servicii, de vinzarea mărfii, contracte de închiriere/comodat, contracte individuale de

- muncă, stabilind condiţiile acestor contracte, va efectua operaţiunile ce se impun cu casa(ele) de marcat, va putea semna contracte de asociere, colaborare, participaţiune, contracte comerciale, cu privire la activitatea societăţii. Va efectua operaţiuni comerciale, va achiziţiona şi distribui marfă, se va ocupa de derularea corespunzătoare a contractelor comerciale/muncă, va angaja/ concedia /disponibiliza personal, va efectua aprovizionarea societăţii, va achiziţiona marfă şi va ocupa inclusiv de buna administrare şi funcţionare a punctului/punctelor de lucru ale societăţii (dacă este cazul);
- dreptul de a îndeplini din numele companiei toate actele procedurale în faţa instanţelor de judecată în orice acţiuni judiciare, având toate drepturile părţii în proces, cu dreptul de a semna şi a depune în judecată cereri de chemare în judecată, cereri de eliberare a ordonanţelor judecătoreşti şi alte acte procesuale necesare, de a strămuta pricina în altă judecată, de a renunţa total sau parţial la pretenţiile din acţiune, de a majora sau reduce cuantumul acestor pretenţii, de a modifica temeiul sau obiectul acţiunii, de a încheia tranzacţii, inclusiv tranzacţii de împăcare, de a intenta acţiune reconvenţională, de a ataca hotărârea judecătorească cu apel şi/sau recurs sau revizuire, de a cere şi de a primi hotărârile, încheierile şi ordonanţele instanţei de judecată şi documentele executorii.
- de a înregistra din numele companiei cereri și demersuri la Agenția Serviciilor Publice (inclusiv la toate Departamentele structurale - Departamentul Cadastru, Departamentul înregistrare și licențiere a unităților de drept, Departamentul înmatriculare a mijloacelor de transport și calificare a conducătorilor auto, Departamentul înregistrare și evidență a populației și alte), și la alte instituții de înregistrare a bunurilor sau a drepturilor, de a semna cereri, contracte și alte acte necesare, de a susține în aceste organe drepturile șu interesele companiei, de a depune, de a solicita, de a primi actele necesare pentru realizarea scopului menționat;
- de a efectua toate actele legate de procedura de executare, inclusiv de prezentare sau retragere a documentului executoriu, de încheiere a tranzacției, de contestare a actelor executorului judecătoresc, de schimbare a modului de executare, de amânare sau eşalonare a executării, de depunere a cererilor, va semna şi va îndeplini toate acţiunile şi formalităţile, necesare pentru atingerea scopului executării silite;
- de a efectua toate acțiunile legate de procedura de insolvabilitate, să participe la toate adunările creditorilor și ședințele comitetului creditorilor si să voteze cu toate voturile pe toate chestiunile de pe ordinea de zi, inclusiv cu drept de vot asupra planului de restructurare, de a fi desemnat în calitate de membru al comitetului creditorilor precum și reprezentant al debitorului;
- are dreptul de a efectua toate acte legate de procedura de executare, inclusiv de primire, prezentare sau de retragere a documentului executoriu, de transmitere a împuternicirilor către o alta persoana (substituire), de încheiere a tranzacției, a reprezenta societatea în procedura de executare cu dreptul de a contesta actele executorului judecătoresc, a semna și depune cerere de calculare și încasare a a dobînzilor, a participa la acțiunile de executare de schimbare a modului de executare, de amanare sau de eșalonare a executarii;
- de a autentifica din numele companiei corespunderea copiei documentului originalului;

Procura este valabilă în decurs de 3 (trei) ani calendaristice de la data eliberării.

Specimenul semnăturii

Administratorul S.R.L. „Lismedfarm” Ecaterina Chitic.