J-C Health Care Ltd.

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פבר' 2019

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ולצרכן של התכשירים:

Intelece 100mg, tablets. Etravirine 100mg 141-29-31789-00
Intelece 200mg, tablets. Etravirine 200mg 149-61-33666-00

הרשומים להתוויה:

Intelence is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced adult patients including those with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance.
Treatment history and when available resistance testing should guide the use of Intelence. In patients who have experienced virological failure on an NNRTI- and nucleoside or nucleotide reverse transcriptase inhibitor (N[t]RTI)- containing regimen Intelence is not recommended for use in combination with N(t)RTIs only.

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

4.4 Special warnings and precautions for use

Immune reconstitution syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable, and these events can occur many months after initiation of treatment (see section 4.8).

4.6 Fertility, **pregnancy and lactation**
Breast-feeding
~~It is not known whether etravirine is excreted in human milk~~. Etravirine is excreted in human milk.
As a general rule, it is recommended that mothers infected by HIV do not breastfeed their babies under any circumstances in order to avoid transmission of HIV.
~~As a general rule, it is recommended that mothers infected by HIV do not breast-feed their babies under any circumstances in order to avoid transmission of HIV.~~

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Fertility
No human data on the effect of etravirine on fertility are available. In rats, there was no effect on mating or fertility with etravirine treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

INTELENCE has ~~no or negligible~~ minor influence on the ability to drive and use machines. No studies on the effects of INTELENCE on the ability to drive or operate machines have been performed. Adverse ~~drug~~ reactions such as somnolence and vertigo have been reported in ~~INTELENCE~~ etravirine treated patients ~~subjects at incidences similar to placebo~~ and should be considered when assessing a patient's ability to drive or operate machinery (see section 4.8). ~~There is no evidence that INTELENCE may alter the patient's ability to drive and operate machines, however, the adverse drug reaction profile should be taken into account.~~

4.8 Undesirable effects

Summary of the safety profile
~~The safety assessment is based on all data from 1,203 patients in the Phase III placebo-controlled trials DUET-1 and DUET-2 in antiretroviral treatment-experienced HIV-1 infected adult patients, 599 of whom received INTELENCE (200 mg b.i.d.) (see section 5.1). In these pooled trials, the median exposure for patients in the INTELENCE arm was 52.3 weeks.~~

~~The most frequently reported adverse drug reactions (ADRs) (incidence ≥ 10% in the INTELENCE arm) of all intensities occurring in the Phase III studies were rash (19.2% in the INTELENCE arm versus 10.9% in the placebo arm), diarrhoea (18.0% in the INTELENCE arm versus 23.5% in the placebo arm), nausea (14.9% in the INTELENCE arm versus 12.7% in the placebo arm) and headache (10.9% in the INTELENCE arm versus 12.7% in the placebo arm). The rates of discontinuation due to any adverse reaction were 7.2% in patients receiving INTELENCE and 5.6% in patients receiving placebo. The most common ADR leading to discontinuation was rash (2.2% in the INTELENCE arm versus 0% in the placebo arm).~~

~~Rash was most frequently mild to moderate, generally macular to maculopapular or erythematous, mostly occurred in the second week of therapy, and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1-2 weeks on continued therapy (see section 4.4). The incidence of rash was higher in women compared to men in the INTELENCE arm in the DUET trials (rash ≥ grade 2 was reported in 9/60 [15.0%] women versus 51/539 [9.5%] men; discontinuations due to rash were reported in 3/60 [5.0%] women versus 10/539 [1.9%] men) (see section 4.4).~~
~~There was no gender difference in severity or treatment discontinuation due to rash. The clinical data are limited and an increased risk of cutaneous reactions in patients with a history of NNRTI-associated cutaneous reaction cannot be excluded (see section 4.4).~~
The most frequent (incidence ≥ 10%) adverse reactions of all intensities reported for etravirine were rash, diarrhoea, nausea and headache. In the Phase III studies, the rates

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of discontinuation due to any adverse reaction were 7.2% in patients receiving etravirine. The most common adverse reaction leading to discontinuation was rash.

Tabulated list of adverse reactions

~~ADRs of moderate intensity or greater (≥ grade 2) reported in patients treated with INTELENCE are summarised in table 2 (background regimen is indicated as "BR"). Laboratory abnormalities considered ADRs are included in a paragraph below table 2. The ADRs are listed by system organ class (SOC) and frequency. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Rare and very rare ADRs cannot be detected based on the number of patients included in the DUET trials.~~

Adverse reactions reported in patients treated with etravirine are summarised in Table 2. The adverse reactions are listed by system organ class (SOC) and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

~~Table 2: DUET-1 and DUET-2 trials~~		
~~System Organ Class (SOC)~~	~~Frequency Category~~	~~ADRs (INTELENCE + BR versus Placebo + BR)~~
~~Blood and lymphatic system disorders~~	~~common~~	~~thrombocytopaenia (1.3% vs 1.5%), anaemia (4.0% vs 3.8%)~~
~~Immune system disorders~~	~~uncommon~~	~~immune reconstitution syndrome (0.2% vs 0.3%), drug hypersensitivity (0.8% vs 1.2%)~~
~~Metabolism and nutrition disorders~~	~~common~~	~~diabetes mellitus (1.3% vs 0.2%), hyperglycaemia (1.5% vs 0.7%), hypercholesterolaemia (4.3% vs 3.6%), hypertriglyceridaemia (6.3% vs 4.3%), hyperlipidaemia (2.5% vs 1.3%)~~
	~~uncommon~~	~~anorexia (0.8% vs 1.5%), dyslipidaemia (0.8% vs 0.3%)~~
~~Psychiatric disorders~~	~~common~~	~~anxiety (1.7% vs 2.6%), insomnia (2.7% vs 2.8%)~~
	~~uncommon~~	~~confusional state (0.2% vs 0.2%), disorientation (0.2% vs 0.3%), nightmares (0.2% vs 0.2%), sleep disorders (0.5% vs 0.5%), nervousness (0.2% vs 0.3%), abnormal dreams (0.2% vs 0.2%)~~
~~Nervous system disorders~~	~~common~~	~~peripheral neuropathy (3.8% vs 2.0%), headache (3.0% vs 4.5%)~~
	~~uncommon~~	~~convulsion (0.5% vs 0.7%), syncope (0.3% vs 0.3%), amnesia (0.3% vs 0.5%), tremor (0.2% vs 0.3%), somnolence (0.7% vs 0.5%), paraesthesia (0.7% vs 0.7%), hypoaesthesia (0.5% vs 0.2%), hypersomnia (0.2% vs 0%), disturbance in attention (0.2% vs 0.2%)~~

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~~Eye disorders~~	~~uncommon~~	~~blurred vision (0.7% vs 0%)~~
~~Ear and labyrinth disorders~~	~~uncommon~~	~~vertigo (0.2% vs 0.5%)~~
~~Cardiac disorders~~	~~common~~	~~myocardial infarction (1.3% vs 0.3%)~~
	~~uncommon~~	~~atrial fibrillation (0.2% vs 0.2%), angina pectoris (0.5% vs 0.3%)~~
~~Vascular disorders~~	~~common~~	~~hypertension (3.2% vs 2.5%)~~
~~Respiratory, thoracic and mediastinal disorders~~	~~uncommon~~	~~bronchospasm (0.2% vs 0%), exertional dyspnoea (0.5% vs 0.5%)~~
~~Gastrointestinal disorders~~	~~common~~	~~gastrooesophageal reflux disease (1.8% vs 1.0%), diarrhoea (7.0% vs 11.3%), vomiting (2.8% vs 2.8%), nausea (5.2% vs 4.8%), abdominal pain (3.5% vs 3.1%), flatulence (1.5% vs 1.0%), gastritis (1.5% vs 1.0%)~~
	~~uncommon~~	~~pancreatitis (0.7% vs 0.3%), haematemesis (0.2% vs 0%), stomatitis (0.2% vs 0.2%), constipation (0.3% vs 0.5%), abdominal distension (0.7% vs 1.0%), dry mouth (0.3% vs 0%), retching (0.2% vs 0%)~~
~~Hepatobiliary disorders~~	~~uncommon~~	~~hepatitis (0.2% vs 0.3%), hepatic steatosis (0.3% vs 0%), cytolytic hepatitis (0.3% vs 0%), hepatomegaly (0.5% vs 0.2%)~~
~~Skin and subcutaneous tissue disorders~~	~~very common~~	~~rash (10.0% vs 3.5%)~~
	~~common~~	~~night sweats (1.0% vs 1.0%)~~
	~~uncommon~~	~~swelling face (0.3% vs 0%), hyperhidrosis (0.5% vs 0.2%), prurigo (0.7% vs 0.5%), dry skin (0.3% vs 0.2%)~~
~~Renal and urinary disorders~~	~~common~~	~~renal failure (2.7% vs 2.0%)~~
~~Reproductive system and breast disorders~~	~~uncommon~~	~~gynaecomastia (0.2% vs 0%)~~
~~General disorders and administration site conditions~~	~~common~~	~~fatigue (3.5% vs 4.6%)~~
	~~uncommon~~	~~sluggishness (0.2% vs 0%)~~

Table 2: Adverse reactions observed with etravirine in clinical trials and post-marketing experience

System Organ Class (SOC)	Frequency category	Adverse Reaction
Blood and lymphatic system disorders	common	thrombocytopaenia, anaemia, decreased neutrophils
	uncommon	decreased white blood cell count
Immune system disorders	common	drug hypersensitivity
	uncommon	immune reconstitution syndrome

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Metabolism and nutrition disorders	common	diabetes mellitus, hyperglycaemia, hypercholesterolaemia, increased low density lipoprotein (LDL), hypertriglyceridaemia, hyperlipidaemia, dyslipidaemia, anorexia
Psychiatric disorders	common	anxiety, insomnia, sleep disorders
	uncommon	confusional state, disorientation, nightmares, nervousness, abnormal dreams
Nervous system disorders	very common	headache
	common	peripheral neuropathy, paraesthesia, hypoaesthesia, amnesia, somnolence
	uncommon	convulsion, syncope tremor, hypersomnia, disturbance in attention
Eye disorders	common	blurred vision
Ear and labyrinth disorders	uncommon	vertigo
Cardiac disorders	common	myocardial infarction
	uncommon	atrial fibrillation, angina pectoris
Vascular disorders	common	hypertension
	rare	haemorrhagic stroke[a]
Respiratory, thoracic and mediastinal disorders	common	exertional dyspnoea
	uncommon	bronchospasm
Gastrointestinal disorders	very common	diarrhoea, nausea
	common	gastrooesophageal reflux disease, vomiting, abdominal pain, abdominal distension, flatulence, gastritis, constipation, dry mouth, stomatitis, lipase increased, blood amylase increased
	uncommon	pancreatitis, haematemesis, retching
Hepatobiliary disorders	common	increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST)
	uncommon	hepatitis, hepatic steatosis, cytolytic hepatitis, hepatomegaly
Skin and subcutaneous tissue disorders	very common	rash
	common	night sweats, dry skin, prurigo
	uncommon	angioneurotic oedema[a], swelling face, hyperhidrosis
	rare	Stevens-Johnson Syndrome[a], erythema multiforme[a]
	very rare	toxic epidermal necrolysis[a], DRESS[b]
Renal and urinary disorders	common	renal failure, blood creatinine increased
Reproductive system and breast disorders	uncommon	gynaecomastia
General disorders and	common	fatigue

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administration site conditions	uncommon	sluggishness

[a] These adverse reactions were observed in other clinical trials than DUET-1 and DUET-2.
[b] These adverse reactions have been identified through postmarketing experience with etravirine.

~~Additional ADRs of at least moderate intensity observed in other trials were angioneurotic oedema, erythema multiforme and haemorrhagic stroke, each reported in no more than 0.5% of patients. Stevens-Johnson Syndrome (rare; < 0.1%) and toxic epidermal necrolysis (very rare; < 0.01%) have been reported during clinical development with INTELENCE.~~

~~*Laboratory abnormalities*~~
~~Treatment emergent clinical laboratory abnormalities (grade 3 or 4), considered ADRs, reported in ≥ 2% of patients in the INTELENCE arm versus the placebo arm, respectively, were increases in amylase (8.9% vs 9.4%), creatinine (2.0% vs 1.7%), lipase (3.4% vs 2.6%), total cholesterol (8.1% vs 5.3%), low density lipoprotein (LDL) (7.2% vs 6.6%), triglycerides (9.2% vs 5.8%), glucose (3.5% vs 2.4%), alanine aminotransferase (ALT) (3.7% vs 2.0%), aspartate amino transferase (AST) (3.2% vs 2.0%) and decreases in neutrophils (5.0% vs 7.4%) and white blood cell count (2.0% vs 4.3%).~~

Description of selected adverse reactions

Rash
Rash was most frequently mild to moderate, generally macular to maculopapular or erythematous, mostly occurred in the second week of therapy, and was infrequent after week 4. Rash was mostly self-limiting, and generally resolved within 1-2 weeks on continued therapy (see section 4.4). The incidence of rash was higher in women compared to men in the etravirine arm in the DUET trials (rash ≥ grade 2 was reported in 9/60 [15.0%] women versus 51/539 [9.5%] men; discontinuations due to rash were reported in 3/60 [5.0%] women versus 10/539 [1.9%] men) (see section 4.4). There was no gender difference in severity or treatment discontinuation due to rash. The clinical data are limited and an increased risk of cutaneous reactions in patients with a history of NNRTI-associated cutaneous reaction cannot be excluded (see section 4.4).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

Immune reconstitution syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

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Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy. The frequency of this is unknown (see section 4.4).

Other special populations
Patients co-infected with hepatitis B and/or hepatitis C virus
In the pooled analysis for DUET-1 and DUET-2, the incidence of hepatic events tended to be higher in co-infected subjects treated with INTELENCE compared to co-infected subjects in the placebo group. INTELENCE should be used with caution in these patients (see also sections 4.4 and 5.2).

~~Adverse drug reactions identified through post marketing experience with INTELENCE~~
~~Hypersensitivity reactions, including DRESS, have been reported with INTELENCE. These hypersensitivity reactions were characterised by rash, fever and sometimes organ involvement (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and eosinophilia) (see section 4.4).~~

השינויים המהותיים בעלון לצרכן מופיעים בסעיפים הבאים:

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

לפני הטיפול באינטלנס, ספר לרופא אם:

(X) משקל ועליה בשומנים ובגלוקוז בדם: במהלך הטיפול נגד נגיף ה HIV, תיתכן עליה במשקל, ברמת השומנים ובגלוקוז בדם. הדבר קשור בחלקו לבריאות מחודשת ולשיבה לאורך החיים ובמקרים מסויימים של שומנים בדם לתרופות נוגדות נגיף ה HIV עצמן. הרופא יבדוק שינויים אלה.

אינטראקציות בין תרופתיות:

(X) אם הינך נוטל אחת מהתרופות הבאות ביחד עם אינטלנס, תיתכן השפעה על פעילותן או פעילות אינטלס. יתכן והמינון של חלק מהתרופות יצטרך להשתנות מכיוון שהשפעתם הרפואית או תופעות הלוואי עלולים להיות מושפעים מהשילוב עם אינטלנס. יש לדווח לרופא אם הנך נוטל אחת מהתרופות הבאות:

(X) דולוטגראביר, מאראבירוק, אמפרבאניר/ריטונאביר ופוסאמפרנאביר/ריטונאביר (תרופות נגודות נגיף ה HIV).

3. כיצד תשתמש בתרופה

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אם הקאת פחות מ 4 שעות לאחר שנטלת אינטלנס, קח טבליה נוספת לאחר ארוחה. אם הקאת יותר מ 4 שעות לאחר ניטל אינטלנס, אין צורך ליטול מנה נוספת עד למועד הבא בו עליך ליטול את התרופה.

4. **תופעות לוואי**

כמו בכל תרופה, השימוש באינטלנס עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן ולא תסבול מאף אחת מהן.

~~במהלך טיפול ב- HIV עלולה להתרחש עלייה במשקל וברמות הליפידים בדם והגלוקוז. הדבר קשור חלקית לשיקום הבריאות ואורח החיים, ובמקרה של הליפידים בדם לעיתים לתרופות ה- HIV עצמן. הרופא יבדוק אותך לשינויים אלה.~~

(X) תופעות לוואי שכיחות מאוד (very common) (תופעות שמופיעות ביותר ממשתמש אחד מעשרה)

פריחה עורית בדרך כלל בדרגה קלה או בינונית. במקרים נדירים דווחה פריחה חמורה שיכולה להיות מסכנת חיים ולכן אם מתפתחת פריחה חשוב לדווח לרופא מיידית על מנת שייעץ לך כיצד לטפל בה והאם יש להפסיק טיפול בתרופה.

כאב ראש

שלשול, בחילה

תופעות לוואי שכיחות (common)(תופעות שמופיעות ב 1-10 משתמשים מתוך 100):

(X) תגובה אלרגית (רגישות יתר)

(X) סכרת, ירידה בתיאבון

(X) חרדה, ישנוניות, חוסר שינה, בעיות שינה.

(X) ~~כאב ראש~~, דקירות או כאב בידיים או ברגליים, חוסר תחושה~~, נדודי שינה, חרדה~~, אובדן תחושה בעור, אובדן זכרון, עייפות.

(X) ראייה מעורפלת

(X) כשל בכליות, לחץ דם גבוה, התקף לב, קוצר נשימה במאמץ.

(X) ~~שלשול, בחילה,~~הקאות, צרבת, כאב בטן, התנפחות באזור הבטן, דלקת בקיבה, גזים, עצירות, דלקת בפה, פה יבש.

(X) ~~כשל כלייתי, לחץ דם גבוה, התקף לב, סוכרת.~~

(X) הזעת לילה, גירוד, עור יבש.

שינוי בערכים של בדיקות דם או שתן. הרופא יסביר לך. למשל: כדוריות אדומות נמוכות.

תופעות לוואי שאינן שכיחות (uncommon) (תופעות שמופיעות ב 1-10 משתמשים מתוך 1,000):

ירידה בספירת תאי דם לבנים

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תסמיני זיהום (כמו קשרי לימפה מוגדלים וחום)

חלומות לא רגילים, בילבול, חוסר התמצאות, עצבנות, סיוטים.

נמנום, רעד, התעלפויות, התקפים, הפרעות קשב.

סחרחורת, כבדות

כאב בחזה /לחץ בחזה, קצב לב לא סדיר

~~אובדן תחושה בעור, נימנום, פרכוסים, אובדן זיכרון, התעלפות, הפרעה בעירנות, ישנוניות, רעד, שבץ~~

~~טישטוש ראייה, סחרחורת, כבדות~~

קשיי נשימה

נ~~פיחות של הבטן,~~ ניסיונות להקיא ללא הצלחה, דלקת הלבלב, ~~עצירות , יובש בפה,~~ הקאה של דם, ~~ניסיון להקיא~~

~~ללא הצלחה~~, ~~דלקת בפה, ירידה בתאבון~~

בעיות בכבד כגון הפאטיטיס, כבד מוגדל.

ג~~רד,~~ הזעה מוגברת~~, יובש בעור~~, התנפחות של הפנים ו/או הגרון.

א~~יטיות בתנועה~~

~~תגובה אלרגית (רגישות יתר), סימפטומים של זיהום (לדוגמא חום ובלוטות לימפה מוגדלות)~~

~~בעיות כבד כגון הפטיטיס~~

התנפחות שדיים בגברים

~~בעיות שינה, חלומות לא שגרתיים, בלבול, חוסר התמצאות, עצבנות.~~

תופעות לוואי נדירות (rare) תופעות שמופיעות ב 1-10 משתמשים מתוך 10,000:

שבץ

תופעות לוואי ששכיחותן לא ידועה (תופעות ששכיחותן טרם נקבעה)

-תגובות רגישות יתר חמורות המאופיינות בפריחה המלווה בחום ובדלקת של איבר כלשהו כגון הפטיטיס.

אם הופיעה תופעת לוואי, אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעת לוואי שלא צויינה בעלון, עליך להתייעץ עם הרופא.

העלון לרופא והעלון לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפסים בפניה אלינו לטלפון 09-9591111 .

בברכה,

צפריר כהן

רוקח ממונה