

J-C Health Care Ltd.

Kibbutz Shefayim 60990, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

מרץ 2016

רופא/ה נכבד/ה
רוקח/ת נכבד/ת

ברצוננו להביא לידיעתכם את העדכונים בעלוניים לרופא ולצרכן של התכשיר:
Intelence 100mg & Intelence 200mg

השינויים מסומנים בעלוניים המצורפים כאשר הטקסט המודגש באדום הוסף לעלון ואילו
הטקסט המחוק בכחול נגרע ממנו.

העלוניים מפורסמים במאגר התרופות שבאתר משרד הבריאות. כמו כן ניתן לקבלו מודפס
על ידי פניה אלינו לטלפון 09-9591111.

להלן העדכונים.

בברכה,

ליליאנה בלטר
רוקחת ממונה

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

עלון לצרכן לפי תקנות הרוקחים (תכשירים) התשמ"ו-1986

התרופה משווקת על פי מרשם רופא בלבד

שם התכשיר וצורתו : אינטלנס 100 מ"ג, אינטלנס 200 מ"ג, טבליות

חומר פעיל וכמותו בכל טבליה

Etravirine 100mg, 200mg

אטרווירין 100 מ"ג, 200 מ"ג

קרא בעיון את העלון עד סופו בטרם תשתמש בתרופה. עלון זה מכיל מידע תמציתי על התרופה. אם יש לך

שאלות נוספות, פנה אל הרופא או אל הרוקח.

תרופה זו נרשמה לטיפול במחלתך. אל תעביר אותה לאחרים. היא עלולה להזיק להם אפילו אם נראה לך כי מחלתם דומה.

אינטלנס מיועדת לטיפול במבוגרים. אינטלנס איננה מיועדת לטיפול במטופלים מתחת לגיל 18 שנים.

תכשיר זה אינו מיועד בדרך כלל למטופלים מעל גיל 65 אלא בהוראת רופא.

1. למה מיועדת התרופה?

אינטלנס מכילה את החומר הפעיל אטראווירין.

אינטלנס היא תרופה המשמשת לטיפול בזיהום בנגיף ה HIV (Human Immunodeficiency Virus) במשולב

עם תרופות אחרות נוגדות נגיף HIV. אינטלנס פועלת באמצעות הורדת רמת הנגיף בגוף, דבר שישפר את

תפקוד המערכת החיסונית ויפחית את הסיכון להתפתחות מחלות הקשורות בזיהום בנגיף ה HIV.

אינטלנס משמשת לטיפול במבוגרים נשאי נגיף ה HIV, אשר טופלו בעבר בתרופות אחרות נוגדות נגיף ה

HIV. ניתן להשתמש באינטלנס לטיפול במטופלים נשאי נגיף ה HIV אשר פיתחו עמידות לתרופות אחרות

מקבוצת ה NNRTIs.

אינטלנס חייבת להילקח בשילוב עם תרופות אחרות נוגדות נגיף ה HIV. יש להוועץ ברופא לגבי שילוב

התרופות המתאים ביותר עבורך.

קבוצה תרופוטי: התרופה שייכת לקבוצת התרופות נוגדות נגיף ה HIV המכונה (NNRTIs) non- inhibitors

nucleoside reverse transcriptase

2. לפני השימוש בתרופה

אין להשתמש בתרופה אם:

~~אל תשתמש בתכשיר כאשר הנך בהריון אלא באישור מפורש מהרופא. אין להניק בזמן השימוש בתכשיר זה.~~

אין להשתמש אם הנך אלרגי לחומר הפעיל אטרורין או לאחד ממרכיבי התרופה האחרים הרשומים בסעיף 6
"מידע נוסף"

אזהרות מיוחדות הנוגעות לשימוש בתרופה:

(X) שוחח עם הרופא המטפל או הרוקח טרם נטילת אינטלנס.

(X) אינטלנס לא מרפאת את הזיהום בנגיף ה HIV, אלא מהווה חלק מטיפול שנועד להפחית את רמת הנגיף

בדם. **גם במהלך הטיפול בתרופה, עדיין אפשר להדביק אחרים ב HIV אם כי הסיכון יורד הודות לטיפול יעיל**

כנגד הנגיף. אינטלנס לא מפחיתה את הסיכון להדבקת אחרים בנגיף ה HIV באמצעות מגע מיני או דם לכן, יש

להמשיך ולהשתמש באמצעי מניעה מתאימים (קונדום או שיטות אחרות המגנות מפני מעבר הנגיף) כדי

להפחית את הסיכון למגע עם נוזלי גוף כמו זרע, הפרשות מהנרתיק או דם, בעת מגע מיני.

יש להוועץ עם הרופא לגבי אמצעי הזהירות הנדרשים בכדי למנוע הדבקת אחרים בנגיף.

(X) גם בזמן נטילת אינטלנס, תתכן התפתחות זיהומים או מחלות אחרות הקשורות בזיהום ב HIV. יש

להקפיד לקיים קשר שוטף עם הרופא המטפל.

(X) תכשיר זה אינו מאושר בישראל במטופלים מתחת לגיל 18

(X) תכשיר זה אינו מיועד בדרך כלל למטופלים מעל גיל 65 אלא בהוראת רופא.

(X) חולים מסויימים ~~עם מחלת HIV מתקדמת~~ הנוטלים קומבינציה של תרופות אנטירטוורליות, ~~שמשך~~

~~הטיפול שלהם ארוך~~, עלולים לפתח מחלת עצם הנקראת אוסטאונקרוזיס (מוות של ריקמת עצם הנגרמת

כתוצאה מאובדן אספקת דם לעצם). משך הטיפול בקומבינציית תרופות אנטירטוורליות, שימוש

בקורטיקוסטרואידים, צריכת אלכוהול, דיכוי חיסוני חמור, מדד מסת גוף גבוה יותר, בין היתר, עלולים להיות

חלק מגורמי הסיכון להתפתחות מחלה זו. תסמינים של אוסטאונקרוזיס הינם קשיחות מפרקים, כאב (בעיקר

בירך, בברך ובכתף) וקושי בתנועה. אם הינך מבחין באחד מתסמינים אלה, עליך ליידע את הרופא.

(X) יש לדווח לרופא אם מתפתחת **פריחה**. במידה ומתפתחת פריחה היא בדרך כלל מופיעה מיד לאחר

התחלת הטיפול נגד נגיף ה HIV ובדרך כלל נעלמת תוך שבוע – שבועיים, גם כאשר ממשיכים להשתמש

בתרופה. לעיתים במהלך הטיפול באינטלנס ייתכן ותתרחש תגובת רגישות יתר (תגובה אלרגית הכוללת פריחה

וחום ואף התנפחות של הפנים, הלשון או הגרון וקשיי נשימה או בליעה) שעלולה להיות מסכנת חיים. יש לדווח

לרופא מיידיית באם אתה חווה תגובת רגישות יתר. הרופא יעץ לך כיצד להתמודד עם התסמינים או האם יש

להפסיק את נטילת התרופה. **אם הפסקת טיפול בגלל תגובת רגישות יתר, אין להתחיל מחדש טיפול באינטלנס.**

(X) יש לדווח לרופא במידה והינך **סובל או סבלת מבעיות בכבד**, כולל הפטיטיס B ו/או C. הרופא שלך יעריך

עד כמה חמורה מחלת הכבד שלך לפני שהוא יחליט האם תיקח את התרופה או לא.

(X) יש לדווח לרופא אם הינך מבחין בשינוי בצורת הגוף או בכמות השומן בגוף. עליה במשקל, אובדן משקל או פיזור שונה מהרגיל של שומן הגוף עלול לקרות אם הנך נוטל שילוב של תרופות נוגדות נגיף ה-HIV.

(X) יש לדווח לרופא מיידית אם הבחנת בתסמיני זיהום או דלקת כלשהם. בחלק מנשאי נגיף ה HIV בשלב מתקדם ובעלי עבר של זיהומים נלווים (opportunistic infections), סימנים ותסמינים של זיהומים קודמים יכולים לבוא לידי ביטוי מיד אחרי התחלת הטיפול בתרופה. יתכן והתסמינים מופיעים בעקבות השיפור בתגובה החיסונית של הגוף ויכולתו להלחם בזיהומים שיתכן והיו נוכחים בגוף ללא תסמינים בולטים.

(X) בנוסף לזיהומים הנלווים (opportunistic infections), בעיות אוטואימוניות (מצב המתרחש כאשר מערכת החיסון תוקפת רקמות גוף בריאות) עלולות גם להתרחש לאחר התחלת נטילת תרופות לטיפול בזיהום ב HIV. בעיות אוטואימוניות יכולות להופיע גם חודשים רבים לאחר התחלת הטיפול. אם הינך מבחין בתסמינים כלשהם של זיהום או תסמינים כגון חולשת שרירים, חולשה המתחילה בידים ובכפות הרגליים אשר עולה מעלה לכיוון מרכז הגוף, דפיקות לב מהירות (פלפיטציה), רעד או היפראקטיביות, יידע את הרופא באופן מידי.

~~אם הינך רגיש/ה למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפני נטילת התרופה.~~

אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח:

ברוב המקרים ניתן לשלב נטילת אינטלנס ותרופות אחרות נוגדות נגיף ה HIV המשתייכות לקבוצה אחרת. עם זאת חלק מהשילובים אינם מומלצים ובמקרים מסויימים יש צורך בהגברת הניטור ו/או שינוי במנת התרופה. אי לכך תמיד יש לדווח לרופא אילו תרופות נוגדות נגיף ה HIV אחרות אתה נוטל, ולמלא את הוראותיו בהירות לגבי התרופות שניתן לשלב. **חשוב לקרוא את העלון לצרכן המצורף לתרופות אלו.**

~~שילוב של אטזאנביר וריטונביר (ניתן לשלב ללא צורך בהתאמת המינון)~~

(X) לא מומלץ ליטול אינטלנס ביחד עם התרופות הבאות:

(X) טיפרנביר/ריטונביר (תרופה לטיפול בזיהון HIV) ~~שילוב של פוסאמפרנביר וריטונביר~~

(X) קרבמזפין, פנוברביטל ופניטואין (לטיפול בפירכוסים)

(X) ריפאמפיצין **בגלל התווית נגד עם מעכבי פרומטאז (boosted protease inhibitors)**, וריפאפנטין (לטיפול

בזיהומים כגון שחפת)

~~(X) עם תכשירים אחרים ממשפחת ה NNRTI (אפאבירנז, נבירפין, דלברדין)~~

(X) עם תכשירים המכילים את הצמח St. John's Wort (הפיריקום פרפורטום) (לטיפול בדיכאון).

יש להוועץ ברופא אם הינך נוטל אחת מתרופות אלו.

(X) אם הינך נוטל אחת מהתרופות הבאות ביחד עם אינטלנס, תיתכן השפעה על פעילותן או פעילות

אינטלנס. יש לדווח לרופא אם הנך נוטל אחת מהתרופות הבאות:

(X) אמידורון, בפרידיל, דיגוקסין, דיזופירמיד, פלקאיניד, לידוקאין, מקסילטין, פרופאפנון או קוינידין (לטיפול בבעיות בלב כגון קצב לב לא תקין).

(X) ורפרין (להפחתת קרישיות הדם), רופאך יורה לך לבצע בדיקות דם.

(X) פלוקונאזול, איטרקונאזול, קטוקונאזול, פוסאקונאזול או וריקונאזול (לטיפול בזיהומים פטרייתיים)

(X) קלאריטרומיצין, ריפאבוטין (אנטיביוטיקה)

(X) ארטמטר/ לומפאנטרין (תרופה לטיפול במלריה)

(X) דיאזפאם (לטיפול בהפרעות שינה ו/או בחרדה)

(X) דקסאמתאזון (קורטיקוסטרואיד לטיפול במגוון מצבים כמו דלקת ותגובה אלרגית)

(X) בוספראויר (תרופה אנטי-זרעית לטיפול בזיהום בהפטיטיס C)

(X) אטורבסטאטין, פלובאסטאטין, לוואסטאטין, פיטאבאסטאטין, רוזורבאסטאטין או סימבאסטטין (להורדת רמת הכולסטרול בדם).

(X) ציקלוספורין, סירולימוס או טקרולימוס (תרופות המדכאות את מערכת החיסון הניתנות בדרכי כלל למניעת דחיית שתל)

(X) סילנדאפיל, ווארדנאפיל או טדאלאפיל (לטיפול בבעיות זיקפה ו/או יתר לחץ דם ראתי)

(X) קלופידוגרל (תרופה למניעת היווצרות קרישי דם)

~~(X) דולוטגראויר (תרופה נגד נגיף ה-HIV)~~

שימוש בתרופה ומזון:

חשוב מאוד ליטול את התרופה לאחר הארוחה. נטילת התרופה על קיבה ריקה פוגעת בספיגתה ומצמצמת את הכמות הנספגת בחצי. למידע נוסף ראה סעיף 3 "כיצד תשתמש בתרופה".

הריון והנקה:

ידעי באופן מיידי את רופאך במידה והנך בהריון.

אין ליטול תרופה זו אם הנך בהריון, אלא אם כן הורה זאת הרופא במפורש.

לנשאות נגיף ה-HIV אסור להניק מאחר וקיים סיכוי להדבקת התינוק בנגיף. היוועצי ברופאך מהי הדרך הבטוחה ביותר להאכיל את תינוקך.

נהיגה ושימוש במכונות:

אין לנהוג או להפעיל מכונות מסוכנות אם הנך מרגיש רדום או מסוחרר לאחר נטילת התרופה.

מידע חשוב על חלק מהמרכיבים של התרופה:

טבלית אינטלנס 100 מכילה לקטוז. בכל טבליה 160 מ"ג לקטוז מונוהידרט.

אם הנך סובל מאי סבילות לסוכרים כמו לקטוז, יש להיוועץ ברופא לפני התחלת השימוש בתרופה.

3. כיצד תשתמש בתרופה

תמיד יש להשתמש לפי הוראות הרופא.

עליך לבדוק עם הרופא או הרוקח אם אינך בטוח.

המינון ואופן הטיפול ייקבעו על ידי הרופא בלבד.

המנה המקובלת הינה 200 מ"ג פעמיים ביום.

אם הנך נוטל טבליות של 100 מ"ג:

בבוקר יש ליטול 2 טבליות אינטלנס 100 מ"ג לאחר הארוחה ובערב יש ליטול 2 טבליות אינטלנס 100 מ"ג לאחר הארוחה.

אם הנך נוטל טבליות של 200 מ"ג:

בבוקר יש ליטול טבליה אחת של אינטלנס 200 מ"ג לאחר הארוחה ובערב יש ליטול טבליה אחת של אינטלנס 200 מ"ג לאחר הארוחה

חשוב מאוד ליטול את התרופה לאחר הארוחה. נטילת התרופה על קיבה ריקה פוגעת בספיגתה ומצמצמת את הכמות הנספגת בחצי. יש להיוועץ ברופא לגבי סוג המזון המתאים.

יש לבלוע את הטבליה בשלמותה עם כוס מים מלאה.

אין לחצות, ללעוס או לכתוש את הטבליה.

אם אינך מסוגל לבלוע את הטבליה בשלמותה, אנא פעל על פי ההוראות הבאות:

-שים את הטבלייה ב-5 מ"ל (כפית) של מים, או לפחות בכמות נוזלים מספקת לכיסוי הטבלייה.

-ערבב היטב עד אשר המים נראים חלביים.

-ניתן להוסיף עוד מים או לחלופין מיץ תפוזים או חלב (אין לשים את הטבליה במיץ תפוזים או חלב לפני הוספת מים תחילה).

-שתה מיד

-שטוף את הכוס מספר פעמים עם מים, מיץ תפוזים או חלב ושתה כל פעם בכדי לוודא כי המנה נלקחה במלואה.

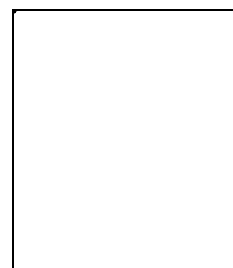
-אין להשתמש במים חמים (מעל 40 מעלות) או במשקאות מוגזים כאשר נוטלים אינטלנס.

אין לעבור על המנה המומלצת.

(X) אם נטלת מעל המנה המומלצת, פנה מיד לרופא או לרוקח.

(X) הוראות לפתיחת הבקבוק : לבקבוק פקק בטחון המונע פתיחה אקראית על ידי ילדים.

יש לפתוח את הבקבוק על ידי לחיצה על הפקק כלפי מטה תוך כדי סיבוב נגד כיוון השעון ולהסיר את הפקק.



(X) אם שכחת ליטול תרופה זו בזמן הקצוב ונזכרת עד 6 שעות מהמועד בו היית צריך ליטול את התרופה, יש ליטול מנה מיד כשנזכרת ותמיד לאחר הארוחה **ולחמשיך ליטול את המנה הבאה כרגיל**. אם עברו יותר מ 6 שעות מהמועד בו היית צריך ליטול את התרופה, יש לדלג על המנה שנשכחה ולהמשיך בנטילת המנה הבאה כרגיל. בשום אופן אין ליטול שתי מנות ביחד בכדי לפצות על מנה שנשכחה! כיצד תוכל לסייע להצלחת הטיפול?

(X) עליך להשלים את הטיפול שהומלץ על ידי הרופא

(X) גם אם חל שיפור במצב בריאותך אין להפסיק הטיפול בתרופה או בתרופות אחרות נוגדות נגיף ה HIV ללא התייעצות עם רופא. **טיפול בנגיף ה HIV עשוי לשפר את תחושת החינניות ואת איכות החיים, אך הפסקת הטיפול ללא אישור הרופא עלולה להגדיל את הסיכון להתפתחות עמידות הנגיף.** אין ליטול תרופות בחושך! בדוק התווית והמנה בכל פעם שהנך נוטל תרופה. הרכב משקפיים אם הנך זקוק להם.

אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.

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.

(X) תופעות המחייבות התייחסות מיוחדת :

במהלך טיפול ב HIV עלול להתרחש עלייה במשקל וברמות הליפידים בדם והגלוקוז. הדבר קשור חלקית

לשיקום הבריאות ואורח חיים, ובמקרה של הליפידים בדם לעיתים לתרופות ה- HIV עצמן. הרופא יבדוק אותך

לשינויים אלה.

(X) נפוך מאוד (דווחו ביותר ממשתמש אחד מתוך 10 משתמשים)

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 שיעץ לך כיצד לטפל בה והאם יש להפסיק טיפול בתרופה.

(X) תופעות לוואי האופייניות לשילוב תרופות נוגדות נגיף ה-HIV:

יש לדווח לרופא אם הינך מבחין בשינוי בצורת הגוף או בכמות השומן בגוף. עליה במשקל, אובדן משקל או פיזור שונה מהרגיל של שומן הגוף עלול לקרות אם הנך נוטל שילוב של תרופות נוגדות נגיף ה-HIV. יש לדווח לרופא מיידית אם הבחנת בתסמיני זיהום כלשהם. בחולים מסוימים במצב מתקדם של זיהום בנגיף ה-HIV ובעלי עבר של זיהומים נלווים (opportunistic infection), סימנים ותסמינים של זיהום קודם יכולים לבוא לידי ביטוי מיד אחרי התחלת הטיפול נוגד הנגיף. יתכן והתסמינים מופיעים בעקבות השיפור בתגובה החיסונית של הגוף ויכולתו להלחם בזיהומים שיתכן והיו נוכחים בגוף ללא תסמינים בולטים. בכל מקרה שבו הנך מרגישה תופעות לוואי שלא צוינו בעלון זה, או אם חל שינוי בהרגשתך הכללית עליך להתייעץ עם הרופא מייד.

(X) בנוסף לזיהומים הנלווים (opportunistic infections) בעיות אוטואימוניות (מצב המתרחש כאשר מערכת החיסון תוקפת רקמות גוף בריאות) עלולות גם להתרחש לאחר התחלת נטילת תרופות לטיפול ב-HIV. בעיות אוטואימוניות יכולות להופיע גם חודשים רבים לאחר התחלת הטיפול. אם הנך מבחין בתסמינים כלשהם של זיהום או תסמינים כגון חולשת שרירים, חולשה המתחילה בידים ובכפות הרגליים אשר עולה מעלה לכיוון מרכז הגוף, דפיקות לב מהירות (פלפיטציה), רעד או היפראקטיביות, ידע את הרופא באופן מידי. תגובה אלרגית חריפה המתבטאת בפריחה עם שלפוחיות על העור, התנפחות הפנים, השפתיים והפה, קשיי נשימה ובלעיה, חום, ידע את הרופא באופן מידי.

סימנים ותסמינים של בעיות בכבד כגון הצהבת העור ולבן העין, שתן כהה, צואה בהירה, בחילה והקאה, אובדן תאבון, כאב בבטן הימנית העליונה.

כאב, רגישות או חולשה של השרירים – אלה עלולים להיות סימנים של פירוק השרירים (rhabdomyolysis). עייפות חריפה, פצעים בפה, דלקת והתנפחות בעיניים.

תופעות לוואי נפוצות (דווחו באחד עד 10 משתמשים מתוך 100 משתמשים):

(X) שינוי בערכי בדיקות הדם, לדוגמא: ספירת כדוריות אדומות נמוכה, ספירת טסיות דם נמוכה, רמות שומנים בדם גבוהות או בלתי תקינות, ערכי כולסטרול גבוהים, רמת סוכר גבוהה.

(X) כאב ראש, דקירות או כאב בידים או ברגליים, חוסר תחושה, נדודי שינה, חרדה, עייפות.

(X) שלשול, בחילה, הקאות, צרבת, כאב בטן, דלקת בקיבה, גזים.

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

(X) שינוי בצורת הגוף או בכמות השומן בגוף, הזעת לילה

(X) שבץ

תופעות לוואי לא נפוצות (דווחו ב עד אחד מתוך 100 משתמשים עד 10 משתמשים מתוך 1000 משתמשים):

כאב בחזה /לחץ בחזה, קצב לב לא סדיר

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

טיטוש ראייה, סחרחורת

קשיי נשימה

נפוחות של הבטן, דלקת הלב, עצירות, יובש בפה, הקאה של דם, ניסיון להקיא ללא הצלחה, דלקת בפה.

גרד, הזעה מוגברת, יובש בעור, התנפחות של הפנים ו/או הגרון.

ירידה בתאבון

איטיות 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.

~~שינוי בצורת הגוף הקשור לשינוי בפזיזור השומן.~~

תופעות לוואי ששכיחותן לא ידועה (לא ניתן להעריכה מהמידע הקיים)

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

~~כאב בשרירים, מתיחות או חולשה. ההפרעות בשרירים יכולות להיות חמורות.~~

~~חלק מתופעות הלוואי אופייניות לתרופות ספציפיות לטיפול בנגיף ה-HIV בין התופעות הללו נכללת immune~~

~~reconstitution syndrome (תסמונת התאוששות של המערכת החיסונית). בחלק מהמטופלים עם זיהום~~

~~מתקדם ב-HIV, והיסטוריה של זיהומים אופורטוניסטים (זיהום שנגרם על ידי אורגניזם שרק לעיתים נדירות~~

~~גורם מחלה באנשים בריאים, אך גורם לעיתים קרובות מחלה באנשים עם מערכת חיסון מוחלשת, לדוגמה,~~

~~בחולים בזיהום ב-HIV, או בחולים שעברו כימותרפיה) וסימנים וסימפטומים של דלקת מזיהומים קודמים יכולים~~

~~להתרחש בסמיכות להתחלת הטיפול בנגיף ה-HIV, כולל באינטלנס.~~

~~בנוסף לזיהומים האופורטוניסטים, הפרעות אוטואימוניות (מצב המתרחש כאשר המערכת החיסונית תוקפת~~

~~רקמות גוף בריאות) יכולות להתרחש אחרי שאתה מתחיל לטול תרופות לטיפול בנגיף ה-HIV. הפרעות~~

~~אוטואימוניות יכולות גם להתרחש הרבה חודשים אחרי הפסקת הטיפול.~~

אם אחת מתופעות הלוואי מחמירה, או כאשר אתה סובל מתופעות לוואי שלא הוזכרו בעלון, עליך להתייעץ עם

הרופא.

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול

תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על

תופעות לוואי, או ע"י כניסה לקישור:

<https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

5. איך לאחסן את התרופה?

מנע הרעלה! תרופה זו וכל תרופה אחרת יש לשמור במקום סגור מחוץ להישג ידם של ילדים ו/או תינוקות ועל ידי- כך תמנע הרעלה. אל תגרום להקאה ללא הוראה מפורשת מהרופא.

אין להשתמש בתרופה אחרי תאריך התפוגה (exp.date) המופיע על גבי האריזה/בקבוק/קרטון/תווית. תאריך התפוגה מתייחס ליום האחרון של אותו חודש.

(X) אין לאחסן מעל 30°C. יש לאחסן את הטבליות בבקבוק המקורי. יש לשמור את הבקבוק סגור היטב על מנת להגן מלחות. הבקבוק מכיל 3 שקיות קטנות המכילות חומר סופח לחות ובכך מאפשרות לשמור על טבליות יבשות. יש להשאיר את השקיות בכל העת בבקבוק. השקיות אינן מיועדות לאכילה.

לאחר פתיחת הבקבוק לראשונה, אין להשתמש בתרופה זו מעבר ל-2 חודשים

6. מידע נוסף

נוסף על החומר הפעיל התרופה מכילה גם:

Intelligence 100: Hypromellose; microcrystalline cellulose; croscarmellose sodium; magnesium stearate; Colloidal anhydrous silica

Lactose monohydrate 160.0mg ובנוסף:

Intelligence 200: Hypromellose; Colloidal anhydrous silica; croscarmellose sodium; magnesium stearate; Silicified microcrystalline Cellulose; microcrystalline cellulose.

כיצד נראית התרופה ומה תוכן האריזה:

אינטלנס 100 מ"ג הינה טבליה אובאלית בצבע לבן - בז' עם הכיתוב T125 בצד אחד והכיתוב 100 בצד השני.

בכל קופסא ישנו בקבוק פלסטיק אחד המכיל 120 טבליות אינטלנס 100 מ"ג. בנוסף בתוך הבקבוק ישנן 3

שקיות קטנות המכילות חומר סופח לחות ובכך מאפשרות לשמור על טבליות יבשות.

אינטלנס 200 מ"ג הינה טבליה מוארכת, קמורה משני צידיה, בצבע לבן – בז', עם הכיתוב T200 בצד אחד.

בבקבוק הפלסטיק מכיל 60 טבליות אינטלנס 200 מ"ג. בנוסף בתוך הבקבוק ישנן 3 שקיות קטנות המכילות

חומר סופח לחות ובכך מאפשרות לשמור על טבליות יבשות.

בעל הרישום: ג"י סי הל' קר בע"מ, קיבוץ שפיים 6099000 ישראל

יצרן: יאנסן סילג, לטינה, איטליה

עלון זה נבדק ואושר ע"י משרד הבריאות בתאריך

מס' רישום התרופה בפנקס התרופות הממלכתי במשרד הבריאות: אינטלנס 100 מ"ג 141293178900

אינטלנס 200 מ"ג: 149613366600

לשם הפשטות ולהקלת הקריאה, עלון זה מנוסח בלשון זכר. על אף זאת, התרופה מיועדת לבני שני המינים.

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

1 NAME OF THE MEDICINAL PRODUCT

INTELENCE™ 100 mg tablets.

INTELENCE™ 200 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

INTELENCE™ 100 mg tablets:

Each tablet contains 100 mg of etravirine.

Excipient: Each tablet contains 160 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

INTELENCE™ 200 mg tablets:

Each tablet contains 200 mg of etravirine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

INTELENCE™ 100 mg tablets:

White to off-white, oval tablet, debossed with "T125" on one side and "100" on the other side

INTELENCE™ 200 mg tablets:

White to off-white, biconvex, oblong tablet debossed with "T200" on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

INTELENCE, in combination with other antiretroviral medicinal products, is indicated 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.

4.2 Posology and method of administration

INTELENCE must always be given in combination with other antiretroviral medicinal products.

Adults

The recommended dose of INTELENCE is 200 mg (one 200 mg tablet or two 100 mg tablets) taken orally twice daily (b.i.d.), following a meal (see section 5.2).

Children (less than 12 years of age) and adolescents (12 to 17 years of age)

Treatment with INTELENCE is not approved **in Israel** in children and adolescents.

Elderly

~~Limited information is available in this population (see sections 4.4 and 5.2).~~

There is limited information regarding the use of INTELENCE in patients > 65 years of age (see section 5.2), therefore caution should be used in this population.

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). **INTELENCE should be used with caution in patients with moderate hepatic impairment.** The pharmacokinetics of INTELENCE have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

Pregnancy and postpartum

Based on limited data available, no dose adjustment is required during pregnancy and postpartum (see section 5.2).

Missed dose

If the patient misses a dose of INTELENCE within 6 hours of the time it is usually taken, the patient should be told to take INTELENCE following a meal as soon as possible and then take the next dose of INTELENCE at the regularly scheduled time. If a patient misses a dose of INTELENCE by more than 6 hours of the time it is usually taken, the patient should be told not to take the missed dose and simply resume the usual dosing schedule.

Method of administration

Patients should be instructed to swallow the tablet(s) as a whole with a liquid such as water. Patients who are unable to swallow the INTELENCE tablet(s) whole may disperse the tablet(s) in a glass of water. The patient should be instructed to do the following:

- place the tablet(s) in 5 ml (1 teaspoon) of water, or at least enough liquid to cover the medicine,
- stir well until the water looks milky;
- if desired, add more water or alternatively orange juice or milk (patients should not place the tablets in orange juice or milk without first adding water);
- drink it immediately;
- rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the patient takes the entire dose.

The use of warm (> 40°C) or carbonated beverages should be avoided.

4.3 Contraindications

Hypersensitivity to etravirine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients should be advised that current antiretroviral therapy does not cure HIV and has not been proven to prevent the transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.

INTELENCE should optimally be combined with other antiretrovirals that exhibit activity against the patient's virus (see section 5.1).

A decreased virologic response to etravirine was observed in patients with viral strains harbouring 3 or more among the following mutations V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S (see section 5.1).

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

No data other than drug-drug interaction data (see section 4.5) are available when etravirine is combined with raltegravir or maraviroc.

~~Clinical studies are ongoing in HIV-1 infected children and adolescents (between the ages of 6 and 17 years, inclusive).~~

Severe Skin and Hypersensitivity Reactions

~~Severe, potentially life-threatening, and fatal skin reactions have been reported with INTELENCE; Stevens-Johnson Syndrome and toxic epidermal necrolysis have been rarely (<0.1%) reported. Hypersensitivity reactions including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have also been reported and were characterized by rash, constitutional findings, and infrequently organ dysfunction, including hepatic failure (see section 4.8).~~

~~Discontinue INTELENCE immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping INTELENCE treatment after the onset of severe rash may result in a life-threatening reaction.~~

Severe cutaneous and hypersensitivity reactions

Severe cutaneous adverse drug reactions have been reported with INTELENCE; Stevens-Johnson Syndrome and erythema multiforme have been rarely (< 0.1%) reported. Treatment with INTELENCE should be discontinued if a severe cutaneous reaction develops.

The clinical data are limited and an increased risk of cutaneous reactions in patients with a history of NNRTI-associated cutaneous reactions cannot be excluded. Caution should be observed in such patients, especially in case of history of a severe cutaneous drug reaction.

Cases of severe hypersensitivity syndromes, including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and TEN (toxic epidermal necrolysis), sometimes fatal, have been reported with the use of INTELENCE (see section 4.8). The DRESS syndrome is characterised by rash, fever, eosinophilia and systemic 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). Time to onset is usually around 3-6 weeks and the outcome in most cases is favourable upon discontinuation and after initiation of corticosteroid therapy.

Patients should be informed to seek medical advice if severe rash or hypersensitivity reactions occur. Patients who are diagnosed with a hypersensitivity reaction whilst on therapy must discontinue INTELENCE immediately.

Delay in stopping INTELENCE treatment after the onset of severe rash may result in a life-threatening reaction.

Patients who have stopped treatment due to hypersensitivity reactions should not restart therapy with INTELENCE.

Rash

Rash has been reported with INTELENCE. Most frequently, rash was mild to moderate, occurred in the second week of therapy and was infrequent after week 4. Rash was mostly self-limiting and generally resolved within 1 to 2 weeks on continued therapy. . **When prescribing INTELENCE to females, prescribers should be aware** The incidence of rash was higher in females (see section 4.8).

Elderly

Experience in geriatric patients is limited: In the Phase III trials, 6 patients aged 65 years or older and 53 patients aged 56-64 years received INTELENCE. The type and incidence of adverse events in patients > 55 years of age were similar to the ones in younger patients (see sections 4.2 and 5.2).

Pregnancy

Given the increased etravirine exposure during pregnancy, caution should be applied for those pregnant patients that require concomitant medications or have comorbidities that may further increase etravirine exposure.

Patients with coexisting conditions

Liver disease

No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). The pharmacokinetics of INTELENCE have not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see sections 4.2 and 5.2).

Renal disease

Since the renal clearance of etravirine is negligible (< 1.2%), a decrease in total body clearance is not expected in patients with renal impairment. No special precautions or dose adjustments are required in patients with renal impairment. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see sections 4.2 and 5.2).

Patients with coexisting conditions

Hepatic impairment

Etravirine is primarily metabolised and eliminated by the liver and highly bound to plasma proteins. Effects on unbound exposure could be expected (has not been studied) and therefore caution is advised in patients with moderate hepatic impairment. INTELENCE has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and its use is therefore not recommended in this group of patients (see sections 4.2 and 5.2).

Co-infection with HBV (hepatitis B virus) or HCV (hepatitis C virus)

Caution should be exercised in patients co-infected with hepatitis B or C virus due to the current limited data available. A potential increased risk of liver enzymes increase cannot be excluded.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Fat redistribution

Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipodystrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution (see section 4.8).

Immune reconstitution syndrome

In HIV infected patients with severe immune deficiency at the time of institution 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 jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

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

Interactions with medicinal products

For information on interactions with medicinal products see section 4.5.

Osteonecrosis

Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Interactions with medicinal products

It is not recommended to combine etravirine with tipranavir/ritonavir, due to a marked pharmacokinetic interaction (76% decrease of etravirine AUC) that could significantly impair the virologic response to etravirine.

For further information on interactions with medicinal products see section 4.5.

Lactose intolerance and lactase deficiency

Each tablet of Intelence 100 mg contains 160 mg of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that affect etravirine exposure

Etravirine is metabolised by cytochrome P450 (CYP) 3A, CYP2C9 and CYP2C19 followed by glucuronidation of the metabolites by uridine diphosphate glucuronosyl transferase (UDPGT). Medicinal products that induce CYP3A, CYP2C9, or CYP2C19 may increase the clearance of etravirine resulting in lowered plasma concentrations of etravirine.

Co-administration of INTELENCE and medicinal products that inhibit CYP3A, CYP2C9, or CYP2C19 may decrease the clearance of etravirine and may result in increased plasma concentrations of etravirine.

Medicinal products that are affected by the use of etravirine

Etravirine is a weak inducer of CYP3A. Co-administration of INTELENCE with medicinal products primarily metabolised by CYP3A may result in decreased plasma concentrations of such medicinal products, which could decrease or shorten their therapeutic effects.

Etravirine is a weak inhibitor of CYP2C9 and CYP2C19. Etravirine is also a weak inhibitor of P-glycoprotein **but not a substrate**. Co-administration with medicinal products primarily metabolised by CYP2C9 or CYP2C19 or transported by P-glycoprotein may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect or **alter their** adverse events profile.

Known and theoretical interactions with selected antiretrovirals and non-antiretroviral medicinal products are listed in the table.1

Interaction table*

Interactions between etravirine and co-administered medicinal products are listed in the table.1 (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, not done as “ND”, once daily as “q.d.”, once daily in the morning as “q.a.m.” and twice daily as “b.i.d.”).

| Drug Interactions—Etravirine co-administered with antiretroviral medicinal products | | | | |
|---|---|--|------|------------------|
| Co-administered Medicinal Product | Dose of Co-administered Medicinal Product (mg) | Medicinal Product Assessed | AUC | C _{min} |
| Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) | | | | |
| NNRTIs (e.g., efavirenz, nevirapine, delavirdine, rilpivirine) | It is not recommended to co-administer INTELENCE with other NNRTIs. | | | |
| Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs/N(t)RTIs) | | | | |
| Didanosine | 400 q.d. | didanosine | ↔ | ND |
| | | etravirine | ↔ | ↔ |
| | | The combination of INTELENCE and didanosine can be used without dose adjustments. As didanosine is administered on an empty stomach, didanosine should be administered one hour before or two hours after INTELENCE (which should be administered following a meal). | | |
| Tenofovir disoproxil fumarate | 300 q.d. | tenofovir | ↔ | ↑19% |
| | | etravirine | ↓19% | ↓18% |

| | | | | |
|---|--|------------|------|------|
| The combination of INTELENCE and tenofovir disoproxil fumarate can be used without dose adjustments. | | | | |
| Other NRTIs | Based on the primarily renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine and zidovudine), no drug interactions are expected between these medicinal products and INTELENCE. | | | |
| HIV Protease Inhibitors (PIs) – Unboosted (i.e., without co-administration of low dose ritonavir) | | | | |
| Atazanavir, unboosted | 400 q.d. | atazanavir | ↓17% | ↓47% |
| | | etravirine | ↑50% | ↑58% |
| It is not recommended to co-administer unboosted atazanavir and INTELENCE. | | | | |
| Ritonavir | Concomitant use of INTELENCE with full dose ritonavir (600 mg b.i.d.) may cause a significant decrease in the plasma concentration of etravirine. This may result in loss of therapeutic effect of INTELENCE. It is not recommended to co-administer full dose ritonavir (600 mg b.i.d.) with INTELENCE. | | | |
| Nelfinavir | Concomitant use of INTELENCE with nelfinavir may cause an increase in the plasma concentrations of nelfinavir. | | | |
| Fosamprenavir, unboosted | Concomitant use of INTELENCE with unboosted fosamprenavir may cause an increase in the plasma concentrations of amprenavir. | | | |
| Other unboosted PIs | It is not recommended to co-administer INTELENCE with other unboosted PIs (including indinavir and saquinavir). | | | |
| HIV Protease Inhibitors (PIs) – Boosted (with low dose ritonavir) | | | | |
| Tipranavir/ritonavir | 500/200 b.i.d. | tipranavir | ↑18% | ↑24% |
| | | etravirine | ↓76% | ↓82% |
| It is not recommended to co-administer tipranavir/ritonavir and INTELENCE. | | | | |
| Fosamprenavir/ritonavir | 700/100 b.i.d. | amprenavir | ↑69% | ↑77% |
| | | etravirine | ↔ | ↔ |
| Amprenavir and fosamprenavir/ritonavir may require dose adjustment when co-administered with INTELENCE. | | | | |
| Atazanavir/ritonavir | 300/100 q.d. | atazanavir | ↓14% | ↓38% |
| | | etravirine | ↑30% | ↑26% |
| The combination of INTELENCE and atazanavir/ritonavir can be used without dose adjustments. | | | | |
| Darunavir/ritonavir | 600/100 b.i.d. | darunavir | ↔ | ↔ |
| | | etravirine | ↓37% | ↓49% |
| The combination of INTELENCE and darunavir/ritonavir can be used without dose adjustments. | | | | |
| Lopinavir/ritonavir (soft gel capsule) | 400/100 b.i.d. | lopinavir | ↓20% | ↓8% |
| | | etravirine | ↑17% | ↑23% |
| The combination of INTELENCE and lopinavir/ritonavir (soft gel capsule) can be used without dose adjustments. | | | | |
| Lopinavir/ritonavir (melt extrusion tablet) | 400/100 b.i.d. | lopinavir | ↔ | ↓20% |
| | | etravirine | ↓35% | ↓45% |

| | | | | |
|---|--------------------------------|--------------|------------|------------|
| The combination of INTELENCE and lopinavir/ritonavir (melt extrusion tablet) can be used without dose adjustments. | | | | |
| Saquinavir/ritonavir (soft-gel capsule) | 1000/100 b.i.d. | saquinavir | ↔ | ↓20% |
| | | etravirine | ↓33% | ↓29% |
| The combination of INTELENCE and saquinavir/ritonavir can be used without dose adjustments. | | | | |
| Dual boosted HIV Protease Inhibitors | | | | |
| Lopinavir/saquinavir/ritonavir | 400/800-1000/100 b.i.d. | lopinavir | ↓18% | ↓24% |
| | | saquinavir | ↓13% | ↓13% |
| | | etravirine | ↔ | ↔ |
| The combination of INTELENCE and lopinavir/saquinavir/ritonavir can be used without dose adjustments. | | | | |
| CCR5 Antagonists | | | | |
| Maraviroc | 300 b.i.d. | maraviroc | ↓53% | ↓39% |
| | | etravirine | ↔ | ↔ |
| Concomitant use of INTELENCE with maraviroc may cause a significant decrease in the plasma concentration of maraviroc. When INTELENCE is co-administered with maraviroc in the absence of a potent CYP3A inhibitor (e.g., a boosted PI), the recommended dose of maraviroc is 600 mg b.i.d. No dose adjustment for INTELENCE is needed. | | | | |
| Maraviroc/darunavir/ritonavir | 150/600/100 b.i.d. | maraviroc | ↑3.1 fold* | ↑5.3 fold* |
| | | etravirine | ↔ | ↔ |
| When INTELENCE is co-administered with maraviroc in the presence of a potent CYP3A inhibitor (e.g., a boosted PI), refer to the applicable prescribing information of maraviroc for the recommended dose, treating INTELENCE as a CYP3A inducer (such as efavirenz). No dose adjustment for INTELENCE is needed. | | | | |
| * compared to maraviroc 150 mg b.i.d. | | | | |
| Fusion Inhibitors | | | | |
| Enfuvirtide | 90 b.i.d. | enfuvirtide | ND | ND |
| | | etravirine* | ↔ | ↔ |
| No interaction is expected for either INTELENCE or enfuvirtide when co-administered. | | | | |
| * based on population pharmacokinetic analysis | | | | |
| Integrase Strand Transfer Inhibitors | | | | |
| Dolutegravir | 50 mg q.d. | dolutegravir | ↓0.29 | ↓0.12 |
| | | etravirine | ↔ | ↔ |
| Dolutegravir/darunavir/ritonavir | 50 mg q.d. + 600/100 mg b.i.d. | dolutegravir | ↓0.75 | ↓0.63 |
| | | etravirine | ↔ | ↔ |
| Dolutegravir/lopinavir/ritonavir | 50 mg q.d. + 400/100 mg b.i.d | dolutegravir | ↔ | ↑1.28 |
| | | etravirine | ↔ | ↔ |

Etravirine significantly reduced plasma concentrations of dolutegravir. The effect of etravirine on dolutegravir plasma concentrations was mitigated by co-administration of darunavir/ritonavir or lopinavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir.

INTELENCE should only be used with dolutegravir when co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. This combination can be used without dose adjustment.

| | | | | |
|------------------------|--------------|---|-------|-------|
| Elvitegravir/ritonavir | 150/100 q.d. | etravirine | ↔ | ND |
| | | ritonavir | ↔ | ND |
| | | etravirine | ↔ | ND |
| | | The combination of INTELENCE and elvitegravir/ritonavir can be used without dose adjustments. | | |
| Raltegravir | 400 b.i.d. | raltegravir | ↓ 10% | ↓ 34% |
| | | etravirine | ↔ | ↔ |
| | | The combination of INTELENCE and raltegravir can be used without dose adjustments. | | |

Drug Interactions—Etravirine co-administered with non-antiretroviral medicinal products

| Etravirine co-administered with non antiretroviral medicinal products | | | | |
|--|--|----------------------------|------|------------------|
| Co-administered Medicinal Product | Dose of Co-administered Medicinal Product (mg) | Medicinal Product Assessed | AUC | C _{min} |
| Antiarrhythmics | | | | |
| Digoxin | 0.5 mg single dose | digoxin | ↑18% | ND |
| | | etravirine | ↔ | ↔ |
| The combination of INTELENCE and digoxin can be used without dose adjustments. It is recommended that digoxin levels be monitored when digoxin is combined with INTELENCE. | | | | |
| Amiodarone Bepridil Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Quinidine | Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with INTELENCE. | | | |
| Anticoagulants | | | | |
| Warfarin | Warfarin concentrations may be affected when co-administered with INTELENCE. It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with INTELENCE. | | | |
| Anticonvulsants | | | | |
| Carbamazepine Phenobarbital Phenytoin | Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE. | | | |
| Antifungals | | | | |

| | | | | |
|---|---|---------------------------|------|-------|
| Fluconazole | 200 q.a.m. | fluconazole | ↔ | ↔ |
| | | etravirine | ↑86% | ↑109% |
| The incidence of adverse events was similar in patients coadministering fluconazole and INTELENCE or placebo in the Phase III trials. The combination of INTELENCE and fluconazole can be used without dose adjustments. | | | | |
| Voriconazole | 200 b.i.d. | voriconazole | ↑14% | ↑23% |
| | | etravirine | ↑36% | ↑52% |
| The combination of INTELENCE and voriconazole can be used without dose adjustments. | | | | |
| Itraconazole | Posaconazole, a potent inhibitor of CYP3A, may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE. The combination of INTELENCE and these antifungals can be used without dose adjustments. | | | |
| Ketoconazole | | | | |
| Posaconazole | | | | |
| Antifungals | | | | |
| Azithromycin | Based on the renal elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE. | | | |
| Clarithromycin | 500 b.i.d. | clarithromycin | ↓39% | ↓53% |
| | | 14-hydroxy-clarithromycin | ↑21% | ↔ |
| | | etravirine | ↑42% | ↑46% |
| Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against <i>Mycobacterium avium</i> complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC. | | | | |
| Antimalarials | | | | |
| Artemether/Lumefantrine [†] | 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours | artemether | ↓38% | ↓18% |
| | | dihydroartemisinin | ↓15% | ↓17% |
| | | lumefantrine | ↓13% | ↔ |
| | | etravirine | ↔ | ↔ |
| No dose adjustment is needed for INTELENCE. Caution is warranted when co-administering INTELENCE and artemether/lumefantrine as it is unknown whether the decrease in exposure of artemether or its active metabolite, dihydroartemisinin, could result in decreased antimalarial efficacy. | | | | |
| Antimycobacterials | | | | |

| | | | | |
|---|--|--|--|--|
| Rifampicin/Rifampin Rifapentine | Rifampicin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE should not be used in combination with rifampicin or rifapentine as co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE. | | | |
| Rifabutin | 300 q.d. | rifabutin 25-O- desacetyl-rifabutin etravirine | ↓17% ↓17% ↓37% | ↓24% ↓22% ↓35% |
| If INTELENCE is not co-administered with a boosted protease inhibitor, then INTELENCE and rifabutin can be used without dose adjustments. If INTELENCE is co-administered with boosted darunavir, lopinavir or saquinavir, then the combination with rifabutin should be used with caution due to the potential for significant reductions in etravirine exposure. When INTELENCE is co-administered with rifabutin and a boosted protease inhibitor, the recommended dose of rifabutin is determined by the prescribing information for the boosted protease inhibitor component of the regimen. | | | | |
| Benzodiazepines | | | | |
| Diazepam | Concomitant use of INTELENCE with diazepam may increase plasma concentrations of diazepam. | | | |
| Corticosteroids | | | | |
| Dexamethasone (systemic) | Systemic dexamethasone induces CYP3A and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use. | | | |
| Estrogen-based Contraceptives | | | | |
| Ethinylestradiol | 0.035 q.d. | ethinylestradiol | ↑22% | ↔ |
| Norethindrone | 1 q.d. | norethindrone etravirine | ↔ ↔ | ↓22% ↔ |
| The combination of estrogen and/or progesterone-based contraceptives and INTELENCE can be used without dose adjustment. | | | | |
| Hepatitis C Virus (HCV) Direct-Acting Antivirals | | | | |
| Boceprevir/Etravirine | 800 mg t.i.d./200mg b.i.d. | boceprevir etravirine | ↑1.10 ↓0.77 | ↓0.88 ↓0.71 |
| The combination of INTELENCE and boceprevir can be used without dose adjustments. Caution should be applied if INTELENCE is co-administered with boceprevir and another drug that potentially decreases etravirine plasma concentrations. Close monitoring for HIV and HCV virologic response is recommended. Please refer to the product information of the associated medications. | | | | |
| Ribavirin | Based on the renal elimination pathway of ribavirin, no drug interactions are expected between ribavirin and INTELENCE. | | | |
| Telaprevir | 750 mg q8h | telaprevir | ↓16% | ↓25% |

| | | | | |
|--|---|------------------------|-------|----|
| | | etravirine | ↔ | ↔ |
| The combination of INTELENCE and telaprevir can be used without dose adjustments. | | | | |
| Herbal Products | | | | |
| St John's wort (<i>Hypericum perforatum</i>) | INTELENCE should not be used concomitantly with products containing St John's wort because co-administration may cause significant decreases in etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE. | | | |
| HMG Co-A Reductase Inhibitors | | | | |
| Atorvastatin | 40 q.d. | atorvastatin | ↓ 37% | ND |
| | | 2-hydroxy-atorvastatin | ↑ 27% | ND |
| | | etravirine | ↔ | ↔ |
| Dose adjustment of atorvastatin may be necessary to tailor the clinical response when combined with INTELENCE. | | | | |
| Fluvastatin | No interaction between pravastatin and INTELENCE is expected. Lovastatin, rosuvastatin and simvastatin are CYP3A substrates and co-administration with INTELENCE may result in lower plasma concentrations of the HMG Co-A reductase inhibitor. Fluvastatin, rosuvastatin and, to a lesser extent, pitavastatin are metabolised by CYP2C9 and co-administration with INTELENCE may result in higher plasma concentrations of the HMG Co-A reductase inhibitor. Dose adjustments for these HMG Co-A reductase inhibitors may be necessary. | | | |
| Lovastatin | | | | |
| Pitavastatin | | | | |
| Pravastatin | | | | |
| Rosuvastatin | | | | |
| Simvastatin | | | | |
| H₂-Receptor Antagonists | | | | |
| Ranitidine | 150 b.i.d. | etravirine | ↓ 14% | ND |
| INTELENCE can be co-administered with H ₂ -receptor antagonists without dose adjustments. | | | | |
| Immunosuppressants | | | | |
| Cyclosporine | Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected when co-administered with INTELENCE. | | | |
| Sirolimus | | | | |
| Tacrolimus | | | | |
| Narcotic Analgesics | | | | |
| Methadone | individual dose ranging from 60 to 130 mg/day | R(-) methadone | ↔ | ↔ |
| | | S(±) methadone | ↔ | ↔ |
| | | etravirine | ↔ | ↔ |
| No changes in methadone dosage were required based on clinical status during or after the period of INTELENCE co-administration. | | | | |
| Phosphodiesterase, type 5 (PDE-5) inhibitors | | | | |
| Sildenafil | 50 mg single dose | sildenafil | ↓ 57% | ND |
| Vardenafil | | N-desmethyl- | ↓ 41% | ND |
| Tadalafil | | sildenafil | | |
| Concomitant use of PDE-5 inhibitors with INTELENCE may require dose adjustment of the PDE-5 inhibitor to attain the desired clinical effect. | | | | |
| Platelet Aggregation Inhibitors | | | | |
| Clopidogrel | Activation of clopidogrel to its active metabolite may be decreased when clopidogrel is co-administered with INTELENCE. Alternatives to clopidogrel should be considered. | | | |

Proton Pump Inhibitors

| | | | | |
|--|---------|------------|------|----|
| Omeprazole | 40 q.d. | etravirine | ↑41% | ND |
| INTELENCE can be co-administered with proton pump inhibitors without dose adjustments. | | | | |

Selective Serotonin Reuptake Inhibitors (SSRIs)

| | | | | |
|--|---------|------------|---|------|
| Paroxetine | 20 q.d. | paroxetine | ↔ | ↓13% |
| | | etravirine | ↔ | ↔ |
| INTELENCE can be co-administered with paroxetine without dose adjustments. | | | | |

* In drug-drug interaction studies, different formulations and/or doses of INTELENCE were used which led to similar exposures and, therefore, interactions relevant for one formulation are relevant for the other.

| Table 1: INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS | | |
|--|---|--|
| Medicinal products by therapeutic areas | Effects on drug levels Least Squares Mean Ratio (90% CI; 1.00 = No effect) | Recommendations concerning co-administration |
| ANTI-INFECTIVES | | |
| Antiretrovirals | | |
| NRTIs | | |
| Didanosine 400 mg once daily | didanosine AUC ↔ 0.99 (0.79-1.25) C _{min} ND C _{max} ↔ 0.91 (0.58-1.42) etravirine AUC ↔ 1.11 (0.99-1.25) C _{min} ↔ 1.05 (0.93-1.18) C _{max} ↔ 1.16 (1.02-1.32) | No significant effect on didanosine and etravirine PK parameters is seen. INTELENCE and didanosine can be used without dose adjustments. |
| Tenofovir disoproxil fumarate 300 mg once daily | tenofovir AUC ↔ 1.15 (1.09-1.21) C _{min} ↑ 1.19 (1.13-1.26) C _{max} ↑ 1.15 (1.04-1.27) etravirine AUC ↓ 0.81 (0.75-0.88) C _{min} ↓ 0.82 (0.73-0.91) C _{max} ↓ 0.81 (0.75-0.88) | No significant effect on tenofovir and etravirine PK parameters is seen. INTELENCE and tenofovir can be used without dose adjustments. |
| Other NRTIs | Not studied, but no interaction expected based on the primary renal elimination route for other NRTIs (e.g., abacavir, emtricitabine, lamivudine, stavudine and zidovudine). | Etravirine can be used with these NRTIs without dose adjustment. |

| | | |
|---|---|--|
| NNRTIs | | |
| Efavirenz Nevirapine Rilpivirine | Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE with efavirenz or nevirapine may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE. Concomitant use of INTELENCE with rilpivirine may cause a decrease in the plasma concentration of rilpivirine and loss of therapeutic effect of rilpivirine. | It is not recommended to co-administer INTELENCE with other NNRTIs. |
| HIV PIs - Unboosted (i.e. without co-administration of low-dose ritonavir) | | |
| Indinavir | Concomitant use of INTELENCE with indinavir may cause a significant decrease in the plasma concentration of indinavir and loss of therapeutic effect of indinavir. | It is not recommended to co-administer INTELENCE with indinavir. |
| Nelfinavir | Not studied. INTELENCE is expected to increase nelfinavir plasma concentrations. | It is not recommended to co-administer INTELENCE with nelfinavir. |
| HIV PIs - Boosted (with low-dose ritonavir) | | |
| Atazanavir/ritonavir 300/100 mg once daily | atazanavir AUC ↓ 0.86 (0.79-0.93) C _{min} ↓ 0.62 (0.55-0.71) C _{max} ↔ 0.97 (0.89-1.05) etravirine AUC ↑ 1.30 (1.18-1.44) C _{min} ↑ 1.26 (1.12-1.42) C _{max} ↑ 1.30 (1.17-1.44) | INTELENCE and atazanavir/ritonavir can be used without dose adjustment. |
| Darunavir/ritonavir 600/100 mg twice daily | darunavir AUC ↔ 1.15 (1.05-1.26) C _{min} ↔ 1.02 (0.90-1.17) C _{max} ↔ 1.11 (1.01-1.22) etravirine AUC ↓ 0.63 (0.54-0.73) C _{min} ↓ 0.51 (0.44-0.61) C _{max} ↓ 0.68 (0.57-0.82) | INTELENCE and darunavir/ritonavir can be used without dose adjustments (see also section 5.1). |
| Fosamprenavir/ritonavir 700/100 mg twice daily | amprenavir AUC ↑ 1.69 (1.53-1.86) C _{min} ↑ 1.77 (1.39-2.25) C _{max} ↑ 1.62 (1.47-1.79) etravirine AUC ↔ ^a C _{min} ↔ ^a C _{max} ↔ ^a | Amprenavir/ritonavir and fosamprenavir/ritonavir may require dose reduction when co-administered with INTELENCE. Using the oral solution may be considered for dose reduction. |
| Lopinavir/ritonavir (tablet) 400/100 mg twice daily | lopinavir AUC ↔ 0.87 (0.83-0.92) C _{min} ↓ 0.80 (0.73-0.88) C _{max} ↔ 0.89 (0.82-0.96) etravirine AUC ↓ 0.65 (0.59-0.71) C _{min} ↓ 0.55 (0.49-0.62) C _{max} ↓ 0.70 (0.64-0.78) | INTELENCE and lopinavir/ritonavir can be used without dose adjustments. |

| | | |
|---|--|---|
| Saquinavir/ritonavir 1,000/100 mg twice daily | saquinavir AUC ↔ 0.95 (0.64-1.42) C _{min} ↓ 0.80 (0.46-1.38) C _{max} ↔ 1.00 (0.70-1.42) etravirine AUC ↓ 0.67 (0.56-0.80) C _{min} ↓ 0.71 (0.58-0.87) C _{max} ↓ 0.63 (0.53-0.75) | INTELENCE and saquinavir/ritonavir can be used without dose adjustments. |
| Tipranavir/ritonavir 500/200 mg twice daily | tipranavir AUC ↑ 1.18 (1.03-1.36) C _{min} ↑ 1.24 (0.96-1.59) C _{max} ↑ 1.14 (1.02-1.27) etravirine AUC ↓ 0.24 (0.18-0.33) C _{min} ↓ 0.18 (0.13-0.25) C _{max} ↓ 0.29 (0.22-0.40) | It is not recommended to co-administer tipranavir/ritonavir and INTELENCE (see section 4.4). |
| CCR5 Antagonists | | |
| Maraviroc 300 mg twice daily Maraviroc/darunavir/ ritonavir 150/600/100 mg twice daily | maraviroc AUC ↓ 0.47 (0.38-0.58) C _{min} ↓ 0.61 (0.53-0.71) C _{max} ↓ 0.40 (0.28-0.57) etravirine AUC ↔ 1.06 (0.99-1.14) C _{min} ↔ 1.08 (0.98-1.19) C _{max} ↔ 1.05 (0.95-1.17) maraviroc* AUC ↑ 3.10 (2.57-3.74) C _{min} ↑ 5.27 (4.51-6.15) C _{max} ↑ 1.77 (1.20-2.60) * compared to maraviroc 150 mg b.i.d. | The recommended dose for maraviroc when combined with INTELENCE in the presence of potent CYP3A inhibitors (e.g. boosted PIs) is 150 mg b.i.d. except for fosamprenavir/ritonavir (maraviroc dose 300 mg b.i.d.). No dose adjustment for INTELENCE is necessary. See also section 4.4. |
| Fusion Inhibitors | | |
| Enfuvirtide 90 mg twice daily | etravirine* AUC ↔ ^a C _{0h} ↔ ^a Enfuvirtide concentrations not studied and no effect is expected. * based on population pharmacokinetic analyses | No interaction is expected for either INTELENCE or enfuvirtide when co-administered. |

| Integrase Strand Transfer Inhibitors | | |
|---|--|--|
| <p>Dolutegravir 50 mg once daily</p> | <p>dolutegravir AUC ↓ 0.29 (0.26-0.34) C_{min} ↓ 0.12 (0.09-0.16) C_{max} ↓ 0.48 (0.43-0.54)</p> <p>etravirine AUC ↔^a C_{min} ↔^a C_{max} ↔^a</p> | <p>Etravirine significantly reduced plasma concentrations of dolutegravir. The effect of etravirine on dolutegravir plasma concentrations was mitigated by co-administration of darunavir/ritonavir or lopinavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir.</p> |
| <p>Dolutegravir + darunavir/ritonavir 50 mg once daily + 600/100 mg twice daily</p> | <p>dolutegravir AUC ↓ 0.75 (0.69-0.81) C_{min} ↓ 0.63 (0.52-0.77) C_{max} ↓ 0.88 (0.78-1.00)</p> <p>etravirine AUC ↔^a C_{min} ↔^a C_{max} ↔^a</p> | <p>INTELENCE should only be used with dolutegravir when co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir. This combination can be used without dose adjustment.</p> |
| <p>Dolutegravir + Lopinavir/ritonavir 50 mg once daily + 400/100 mg twice daily</p> | <p>dolutegravir AUC ↔ 1.11 (1.02-1.20) C_{min} ↑ 1.28 (1.13-1.45) C_{max} ↔ 1.07 (1.02-1.13)</p> <p>etravirine AUC ↔^a C_{min} ↔^a C_{max} ↔^a</p> | |
| <p>Raltegravir 400 mg twice daily</p> | <p>raltegravir AUC ↓ 0.90 (0.68-1.18) C_{min} ↓ 0.66 (0.34-1.26) C_{max} ↓ 0.89 (0.68-1.15)</p> <p>etravirine AUC ↔ 1.10 (1.03-1.16) C_{min} ↔ 1.17 (1.10-1.26) C_{max} ↔ 1.04 (0.97-1.12)</p> | <p>INTELENCE and raltegravir can be used without dose adjustments.</p> |
| ANTIARRHYTHMICS | | |
| <p>Digoxin 0.5 mg single dose</p> | <p>digoxin AUC ↑ 1.18 (0.90-1.56) C_{min} ND C_{max} ↑ 1.19 (0.96-1.49)</p> | <p>INTELENCE and digoxin can be used without dose adjustments. It is recommended that digoxin levels be monitored when digoxin is combined with INTELENCE.</p> |
| <p>Amiodarone Bepiridil Disopyramide Flecainide Lidocaine (systemic) Mexiletine Propafenone Quinidine</p> | <p>Not studied. INTELENCE is expected to decrease plasma concentrations of these antiarrhythmics.</p> | <p>Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with INTELENCE.</p> |

| ANTIBIOTICS | | |
|---|---|---|
| Azithromycin | Not studied. Based on the biliary elimination pathway of azithromycin, no drug interactions are expected between azithromycin and INTELENCE. | INTELENCE and azithromycin can be used without dose adjustments. |
| Clarithromycin 500 mg twice daily | clarithromycin AUC ↓ 0.61 (0.53-0.69) C _{min} ↓ 0.47 (0.38-0.57) C _{max} ↓ 0.66 (0.57-0.77) 14-OH-clarithromycin AUC ↑ 1.21 (1.05-1.39) C _{min} ↔ 1.05 (0.90-1.22) C _{max} ↑ 1.33 (1.13-1.56) etravirine AUC ↑ 1.42 (1.34-1.50) C _{min} ↑ 1.46 (1.36-1.58) C _{max} ↑ 1.46 (1.38-1.56) | Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against <i>Mycobacterium avium</i> complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC. |
| ANTICOAGULANTS | | |
| Warfarin | Not studied. INTELENCE is expected to increase plasma concentrations of warfarin. | It is recommended that the international normalised ratio (INR) be monitored when warfarin is combined with INTELENCE. |
| ANTICONVULSANTS | | |
| Carbamazepine Phenobarbital Phenytoin | Not studied. Carbamazepine, phenobarbital and phenytoin are expected to decrease plasma concentrations of etravirine. | Combination not recommended. |
| ANTIFUNGALS | | |
| Fluconazole 200 mg once in the morning | fluconazole AUC ↔ 0.94 (0.88-1.01) C _{min} ↔ 0.91 (0.84-0.98) C _{max} ↔ 0.92 (0.85-1.00) etravirine AUC ↑ 1.86 (1.73-2.00) C _{min} ↑ 2.09 (1.90-2.31) C _{max} ↑ 1.75 (1.60-1.91) | INTELENCE and fluconazole can be used without dose adjustments. |
| Itraconazole Ketoconazole Posaconazole | Not studied. Posaconazole, a potent inhibitor of CYP3A4, may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE. | INTELENCE and these antifungals can be used without dose adjustments. |

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|---|---|---|
| Voriconazole 200 mg twice daily | <p><u>voriconazole</u> AUC ↑ 1.14 (0.88-1.47) C_{min} ↑ 1.23 (0.87-1.75) C_{max} ↓ 0.95 (0.75-1.21)</p> <p><u>etravirine</u> AUC ↑ 1.36 (1.25-1.47) C_{min} ↑ 1.52 (1.41-1.64) C_{max} ↑ 1.26 (1.16-1.38)</p> | INTELENCE and voriconazole can be used without dose adjustments. |
| ANTIMALARIALS | | |
| Artemether/ Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours | <p><u>artemether</u> AUC ↓ 0.62 (0.48-0.80) C_{min} ↓ 0.82 (0.67-1.01) C_{max} ↓ 0.72 (0.55-0.94)</p> <p><u>dihydroartemisinin</u> AUC ↓ 0.85 (0.75-0.97) C_{min} ↓ 0.83 (0.71-0.97) C_{max} ↓ 0.84 (0.71-0.99)</p> <p><u>lumefantrine</u> AUC ↓ 0.87 (0.77-0.98) C_{min} ↔ 0.97 (0.83-1.15) C_{max} ↔ 1.07 (0.94-1.23)</p> <p><u>etravirine</u> AUC ↔ 1.10 (1.06-1.15) C_{min} ↔ 1.08 (1.04-1.14) C_{max} ↔ 1.11 (1.06-1.17)</p> | Close monitoring of antimalarial response is warranted when co-administering INTELENCE and artemether/lumefantrine as a significant decrease in exposure of artemether and its active metabolite, dihydroartemisinin, may result in decreased antimalarial efficacy. No dose adjustment is needed for INTELENCE. |
| ANTIMYCOBACTERIALS | | |
| Rifampicin Rifapentine | Not studied. Rifampicin and rifapentine are expected to decrease plasma concentrations of etravirine. INTELENCE should be used in combination with a boosted protease inhibitor (PI). Rifampicin is contraindicated in combination with boosted PIs. | Combination not recommended. |
| Rifabutin 300 mg once daily | <p>With an associated boosted PI: No interaction study has been performed. Based on historical data, a decrease in etravirine exposure may be expected whereas an increase in rifabutin exposure and especially in 25-O-desacetyl-rifabutin may be expected.</p> <p>With no associated boosted PI (out of the recommended indication for etravirine): <u>rifabutin</u> AUC ↓ 0.83 (0.75-0.94) C_{min} ↓ 0.76 (0.66-0.87) C_{max} ↓ 0.90 (0.78-1.03) <u>25-O-desacetyl-rifabutin</u> AUC ↓ 0.83 (0.74-0.92) C_{min} ↓ 0.78 (0.70-0.87) C_{max} ↓ 0.85 (0.72-1.00) <u>etravirine</u> AUC ↓ 0.63 (0.54-0.74) C_{min} ↓ 0.65 (0.56-0.74) C_{max} ↓ 0.63 (0.53-0.74)</p> | <p>The combination of INTELENCE with a boosted PI and rifabutin should be used with caution due to the risk of decrease in etravirine exposure and the risk of increase in rifabutin and 25-O-desacetyl-rifabutin exposures.</p> <p>Close monitoring for virologic response and for rifabutin related adverse reactions is recommended. Please refer to the product information of the associated boosted PI for the dose adjustment of rifabutin to be used.</p> |

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| BENZODIAZEPINES | | |
| Diazepam | Not studied. Etravirine is expected to increase plasma concentrations of diazepam. | Alternatives to diazepam should be considered. |
| CORTICOSTEROIDS | | |
| Dexamethasone (systemic) | Not studied. Dexamethasone is expected to decrease plasma concentrations of etravirine | Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for chronic use. |
| OESTROGEN-BASED CONTRACEPTIVES | | |
| Ethinylestradiol 0.035 mg once daily Norethindrone 1 mg once daily | ethinylestradiol AUC ↑ 1.22 (1.13-1.31) C _{min} ↔ 1.09 (1.01-1.18) C _{max} ↑ 1.33 (1.21-1.46) norethindrone AUC ↔ 0.95 (0.90-0.99) C _{min} ↓ 0.78 (0.68-0.90) C _{max} ↔ 1.05 (0.98-1.12) etravirine AUC ↔ ^a C _{min} ↔ ^a C _{max} ↔ ^a | The combination of oestrogen- and/or progesterone-based contraceptives and INTELENCE can be used without dose adjustment. |
| HEPATITIS C VIRUS (HCV) DIRECT-ACTING ANTIVIRALS | | |
| Ribavirin | Not studied, but no interaction expected based on the renal elimination pathway of ribavirin. | The combination of INTELENCE and ribavirin can be used without dose adjustments. |
| Boceprevir Boceprevir 800 mg 3 times daily + etravirine 200 mg every 12 hours | boceprevir AUC ↑ 1.10 (0.94-1.28) C _{max} ↑ 1.10 (0.94-1.29) C _{min} ↓ 0.88 (0.66-1.17) etravirine AUC ↓ 0.77 (0.66-0.91) C _{max} ↓ 0.76 (0.68-0.85) C _{min} ↓ 0.71 (0.54-0.95) | The clinical significance of the reductions in etravirine pharmacokinetic parameters and boceprevir C _{min} in the setting of the combination therapy with HIV antiretroviral medicines which also affect the pharmacokinetics of etravirine and/or boceprevir has not been directly assessed. Increased clinical and laboratory monitoring for HIV and HCV suppression is recommended. |
| Telaprevir 750 mg every 8 hours | telaprevir AUC ↓ 0.84 (0.71-0.98) C _{max} ↓ 0.90 (0.79-1.02) C _{min} ↓ 0.75 (0.61-0.92) etravirine AUC ↔ 0.94 (0.85-1.04) C _{max} ↔ 0.93 (0.84-1.03) C _{min} ↔ 0.97 (0.86-1.10) | The combination of INTELENCE and telaprevir can be used without dose adjustments. |
| HERBAL PRODUCTS | | |
| St John's wort (<i>Hypericum perforatum</i>) | Not studied. St John's wort is expected to decrease the plasma concentrations of etravirine. | Combination not recommended. |

| HMG CO-A REDUCTASE INHIBITORS | | |
|---|--|--|
| Atorvastatin 40 mg once daily | atorvastatin AUC ↓ 0.63 (0.58-0.68) C _{min} ND C _{max} ↑ 1.04 (0.84-1.30) 2-OH-atorvastatin AUC ↑ 1.27 (1.19-1.36) C _{min} ND C _{max} ↑ 1.76 (1.60-1.94) etravirine AUC ↔ 1.02 (0.97-1.07) C _{min} ↔ 1.10 (1.02-1.19) C _{max} ↔ 0.97 (0.93-1.02) | The combination of INTELENCE and atorvastatin can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on clinical response. |
| Fluvastatin Lovastatin Pravastatin Rosuvastatin Simvastatin | Not studied. No interaction between pravastatin and INTELENCE is expected. Lovastatin, rosuvastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE may result in lower plasma concentrations of the HMG Co-A reductase inhibitor. Fluvastatin, and rosuvastatin are metabolised by CYP2C9 and co-administration with INTELENCE may result in higher plasma concentrations of the HMG Co-A reductase inhibitor. | Dose adjustments for these HMG Co-A reductase inhibitors may be necessary. |
| H₂-RECEPTOR ANTAGONISTS | | |
| Ranitidine 150 mg twice daily | etravirine AUC ↓ 0.86 (0.76-0.97) C _{min} ND C _{max} ↓ 0.94 (0.75-1.17) | INTELENCE can be co-administered with H ₂ -receptor antagonists without dose adjustments. |
| IMMUNOSUPPRESSANTS | | |
| Cyclosporin Sirolimus Tacrolimus | Not studied. Etravirine is expected to decrease plasma concentrations of cyclosporine, sirolimus and tacrolimus. | Co-administration with systemic immunosuppressants should be done with caution because plasma concentrations of cyclosporin, sirolimus and tacrolimus may be affected when co-administered with INTELENCE. |
| NARCOTIC ANALGESICS | | |
| Methadone individual dose ranging from 60 mg to 130 mg once daily | R(-) methadone AUC ↔ 1.06 (0.99-1.13) C _{min} ↔ 1.10 (1.02-1.19) C _{max} ↔ 1.02 (0.96-1.09) S(+) methadone AUC ↔ 0.89 (0.82-0.96) C _{min} ↔ 0.89 (0.81-0.98) C _{max} ↔ 0.89 (0.83-0.97) etravirine AUC ↔ ^a C _{min} ↔ ^a C _{max} ↔ ^a | No changes in methadone dosage were required based on clinical status during or after the period of INTELENCE co-administration. |

| PHOSPHODIESTERASE, TYPE 5 (PDE-5) INHIBITORS | | |
|---|--|--|
| Sildenafil 50 mg single dose Tadalafil Vardenafil | sildenafil AUC ↓ 0.43 (0.36-0.51) C _{min} ND C _{max} ↓ 0.55 (0.40-0.75) N-desmethyl-sildenafil AUC ↓ 0.59 (0.52-0.68) C _{min} ND C _{max} ↓ 0.75 (0.59-0.96) | Concomitant use of PDE-5 inhibitors with INTELENCE may require dose adjustment of the PDE-5 inhibitor to attain the desired clinical effect. |
| PLATELET AGGREGATION INHIBITORS | | |
| Clopidogrel | <i>In vitro</i> data show that etravirine has inhibitory properties on CYP2C19. It is therefore possible that etravirine may inhibit the metabolism of clopidogrel to its active metabolite by such inhibition of CYP2C19 <i>in vivo</i> . The clinical relevance of this interaction has not been demonstrated. | As a precaution it is recommended that concomitant use of etravirine and clopidogrel should be discouraged. |
| PROTON PUMP INHIBITORS | | |
| Omeprazole 40 mg once daily | etravirine AUC ↑ 1.41 (1.22-1.62) C _{min} ND C _{max} ↑ 1.17 (0.96-1.43) | INTELENCE can be co-administered with proton pump inhibitors without dose adjustments. |
| SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) | | |
| Paroxetine 20 mg once daily | paroxetine AUC ↔ 1.03 (0.90-1.18) C _{min} ↓ 0.87 (0.75-1.02) C _{max} ↔ 1.06 (0.95-1.20) etravirine AUC ↔ 1.01 (0.93-1.10) C _{min} ↔ 1.07 (0.98-1.17) C _{max} ↔ 1.05 (0.96-1.15) | INTELENCE can be co-administered with paroxetine without dose adjustments. |

^a Comparison based on historic control.

Note: In drug-drug interaction studies, different formulations and/or doses of etravirine were used which led to similar exposures and, therefore, interactions relevant for one formulation are relevant for the other.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy

~~There are no adequate and well-controlled studies with etravirine in pregnant women. Studies in animals have not shown evidence of developmental toxicity or effect on reproductive function and fertility (see section 5.3).~~

~~INTELENCE should be used during pregnancy only if the potential benefit justifies the potential risk.~~

As a general rule, when deciding to use antiretroviral agents for the treatment of HIV infection in pregnant women, and consequently for reducing the risk of HIV vertical transmission to the newborn, the animal data as well as the clinical experience in pregnant women should be taken into account in order to characterise the safety for the foetus.

Placental transfer has been seen in pregnant rats, but it is not known whether placental transfer of INTELENCE also occurs in pregnant women. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Based on animal data the malformative risk is unlikely in humans. The clinical data do not raise safety concern but are very limited.

Lactation

It is not known whether etravirine is excreted in human milk.

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.

Fertility

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

4.7 Effects on ability to drive and use machines

~~No studies on the effects of INTELENCE on the ability to drive or operate machines have been performed. There is no evidence that INTELENCE may alter the patient's ability to drive and operate machines, however, the adverse drug reaction profile of INTELENCE should be taken into account (see section 4.8).~~

INTELENCE has no or negligible influence on the ability to drive and use machines. Adverse drug reactions such as somnolence and vertigo have been reported in INTELENCE treated subjects at incidences similar to placebo (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

Adverse Drug Reactions from Clinical Trials

The safety assessment is based on all data from 1203 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 ~~and placebo arm~~ was 52.3 ~~and 51.0 weeks, respectively.~~

~~The most frequently reported adverse drug reactions (ADRs) ($\geq 5\%$) that were at least grade 2 in severity were rash (10.0% in the INTELENCE arm and 3.5% in the placebo arm), diarrhoea (7.0% in the INTELENCE arm and 11.3% in the placebo arm), hypertriglyceridaemia (6.3% in the INTELENCE arm and 4.3% in the placebo arm) and nausea (5.2% in the INTELENCE arm and 4.8% in the placebo arm) (see table below).~~

~~The majority of the ADRs reported during treatment with INTELENCE were grade 1 to 2 in severity. Grade 3 or 4 ADRs were reported in 22.2% and 17.2% of the INTELENCE and placebo treated patients, respectively. The most commonly reported grade 3 or 4 ADRs were hypertriglyceridaemia (4.2% in the INTELENCE arm and 2.3% in the placebo arm), hypercholesterolaemia (2.2% in the INTELENCE arm~~

and 2.3% in the placebo arm), renal failure (2.0% in the INTELENCE arm and 1.2% in the placebo arm) and anaemia (1.7% in the INTELENCE arm and 1.3% in the placebo arm). For treatment emergent clinical laboratory abnormalities (grade 3 or 4) reported in greater than or equal to 2% of INTELENCE treated patients, see table “Treatment Emergent Laboratory Abnormalities”. All other grade 3 and/or 4 ADRs were reported in less than 1.5% of the INTELENCE treated patients. 5.2% of patients in the INTELENCE arm discontinued treatment due to ADRs compared to 2.6% of patients in the placebo arm. The most common ADR leading to discontinuation was rash (2.2% in the INTELENCE arm versus 0% in the placebo arm).

The most frequently reported adverse drug reactions (ADRs) (incidence $\geq 10\%$ 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 \geq 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). ~~In patients with a history of NNRTI-related rash, there was no apparent increased risk for the development of INTELENCE-related rash compared to patients without a history of NNRTI-related rash.~~

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).

Tabulated list of adverse reactions

ADRs of moderate intensity or greater (\geq 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$). Rare and very rare ADRs cannot be detected based on the number of patients included in the DUET trials.

| 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%) |
| 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%) |

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 $\geq 2\%$ 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

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) 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).

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).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

ADRs of moderate intensity or greater (\geq grade 2) and reported in $\geq 1\%$ of patients treated with INTELENCE are summarised in the table below. The ADRs are listed by system organ class (SOC) and frequency. Laboratory abnormalities considered ADRs are included in a table below (see Treatment Emergent Grade 3 to 4 Laboratory Abnormalities Reported in $\geq 2\%$ of Patients).

| ADRs of moderate intensity or greater (\geq grade 2) and reported in $\geq 1\%$ of adult patients treated with INTELENCE | | |
|---|-----------------------|---------------------|
| DUET-1 and DUET-2 Trials | | |
| System Organ Class (SOC) | INTELENCE + BR | Placebo + BR |
| Adverse Drug Reaction | N=599 | N=604 |
| Cardiac disorders | | |
| Myocardial infarction | 1.3% | 0.3% |
| Blood and lymphatic system disorders | | |
| Anaemia | 4.0% | 3.8% |
| Thrombocytopaenia | 1.3% | 1.5% |
| Nervous system disorders | | |
| Peripheral neuropathy | 3.8% | 2.0% |
| Headache | 3.0% | 4.5% |
| Gastrointestinal disorders | | |
| Diarrhoea | 7.0% | 11.3% |
| Nausea | 5.2% | 4.8% |
| Abdominal pain | 3.5% | 3.1% |
| Vomiting | 2.8% | 2.8% |
| Gastroesophageal reflux disease | 1.8% | 1.0% |
| Flatulence | 1.5% | 1.0% |
| Gastritis | 1.5% | 1.0% |
| Renal and urinary disorders | | |
| Renal failure | 2.7% | 2.0% |
| Skin and subcutaneous tissue disorders | | |
| Rash | 10.0% | 3.5% |
| Lipohypertrophy | 1.0% | 0.3% |

| | | |
|---|------|------|
| Night sweats | 1.0% | 1.0% |
| Metabolism and nutrition disorders | | |
| Hypertriglyceridaemia | 6.3% | 4.3% |
| Hypercholesterolaemia | 4.3% | 3.6% |
| Hyperlipidaemia | 2.5% | 1.3% |
| Hyperglycaemia | 1.5% | 0.7% |
| Diabetes mellitus | 1.3% | 0.2% |
| Vascular disorders | | |
| Hypertension | 3.2% | 2.5% |
| General disorders and administration site conditions | | |
| Fatigue | 3.5% | 4.6% |
| Psychiatric disorders | | |
| Insomnia | 2.7% | 2.8% |
| Anxiety | 1.7% | 2.6% |

Treatment emergent ADRs of moderate intensity or greater (\geq grade 2) and occurring in less than 1% of patients receiving INTELENCE were:

- cardiac disorders: angina pectoris, atrial fibrillation
- nervous system disorders: paraesthesia, somnolence, convulsion, hypoaesthesia, amnesia, syncope, disturbance in attention, hypersomnia, tremor
- eye disorders: blurred vision
- ear and labyrinth disorders: vertigo
- respiratory, thoracic and mediastinal disorders: exertional dyspnoea, bronchospasm
- gastrointestinal disorders: abdominal distension, pancreatitis, constipation, dry mouth, haematemesis, retching, stomatitis
- skin and subcutaneous tissue disorders: prurigo, hyperhidrosis, dry skin, swelling face
- metabolism and nutrition disorders: anorexia, dyslipidaemia
- general disorders and administration site conditions: sluggishness
- immune system disorders: drug hypersensitivity, immune reconstitution syndrome
- hepatobiliary disorders: hepatomegaly, cytolytic hepatitis, hepatic steatosis, hepatitis
- reproductive system and breast disorders: gynaecomastia
- psychiatric disorders: sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares

Additional ADRs of at least moderate intensity observed in other trials were acquired lipodystrophy, angioneurotic edema, 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 $\geq 2\%$ of INTELENCE-treated patients are shown in the table below.

| Treatment emergent grade 3 to 4 laboratory abnormalities reported in $\geq 2\%$ of patients | | | |
|---|-------------------------|-------------------------|-----------------------|
| Pooled DUET-1 and DUET-2 Trials | | | |
| Laboratory Parameter Preferred Term, n (%) | DAIDS Toxicity Range | INTELENCE + BR N=599 | Placebo + BR N=604 |
| GENERAL BIOCHEMISTRY | | | |

| | | | |
|---------------------------------------|---|-----------------|-----------------|
| Pancreatic Amylase | | 53 (8.9) | 57 (9.4) |
| grade 3 | > 2-5 x ULN | 44 (7.4) | 51 (8.4) |
| grade 4 | > 5 x ULN | 9 (1.5) | 6 (1.0) |
| Creatinine | | 12 (2.0) | 10 (1.7) |
| grade 3 | > 1.9-3.4 x ULN | 12 (2.0) | 9 (1.5) |
| grade 4 | > 3.4 x ULN | 0 (0) | 1 (0.2) |
| Lipase | | 20 (3.4) | 16 (2.6) |
| grade 3 | > 3-5 x ULN | 12 (2.0) | 13 (2.2) |
| grade 4 | > 5 x ULN | 8 (1.3) | 3 (0.5) |
| GENERAL HEMATOLOGY | | | |
| White blood cell count | | 12 (2.0) | 26 (4.3) |
| grade 3 | 1.0-1,499 giga/l 1,000-1,499/mm ³ | 6 (1.0) | 22 (3.6) |
| grade 4 | < 1.0 giga/l < 1,000/mm ³ | 6 (1.0) | 4 (0.7) |
| HEMATOLOGY DIFFERENTIAL COUNTS | | | |
| Neutrophils | | 30 (5.1) | 45 (7.5) |
| grade 3 | 0.5-0.749 giga/l 500-749/mm ³ | 21 (3.5) | 26 (4.3) |
| grade 4 | < 0.5 giga/l < 500/mm ³ | 9 (1.5) | 19 (3.1) |
| LIPIDS AND GLUCOSE | | | |
| Total cholesterol | | 48 (8.1) | 32 (5.3) |
| grade 3 | > 7.77 mmol/l > 300 mg/dl | 48 (8.1) | 32 (5.3) |
| Low density lipoprotein | | 42 (7.2) | 39 (6.6) |
| grade 3 | > 4.9 mmol/l > 190 mg/dl | 42 (7.2) | 39 (6.6) |
| Triglycerides | | 55 (9.2) | 35 (5.8) |
| grade 3 | 8.49-13.56 mmol/l 751-1200 mg/dl | 34 (5.7) | 24 (4.0) |
| grade 4 | > 13.56 mmol/l > 1200 mg/dl | 21 (3.5) | 11 (1.8) |
| Elevated Glucose Levels | | 21 (3.5) | 14 (2.3) |
| grade 3 | 13.89-27.75 mmol/l 251-500 mg/dl | 21 (3.5) | 13 (2.2) |
| grade 4 | > 27.75 mmol/l > 500 mg/dl | 0 (0) | 1 (0.2) |
| HEPATIC PARAMETERS | | | |
| Alanine amino transferase | | 22 (3.7) | 12 (2.0) |
| grade 3 | 5.1-10 x ULN | 16 (2.7) | 10 (1.7) |
| grade 4 | > 10 x ULN | 6 (1.0) | 2 (0.3) |
| Aspartate amino transferase | | 19 (3.2) | 12 (2.0) |
| grade 3 | 5.1-10 x ULN | 16 (2.7) | 10 (1.7) |
| grade 4 | > 10 x ULN | 3 (0.5) | 2 (0.3) |

ULN=Upper Limit of Normal

Lipodystrophy

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorso-cervical fat accumulation (buffalo hump) (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 (immune reconstitution syndrome). Autoimmune disorders such as Graves' disease have also been reported in the context of Immune Reconstitution syndrome, the reported time to onset is more variable and these events can occur many months after initiation of treatment. (see section 4.4).

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).

Additional information on special populations

Patients co-infected with hepatitis B and/or hepatitis C virus

Among co-infected patients (n=139) in the pooled analysis for DUET-1 and DUET-2, grade 3 or 4 elevations in AST developed in 9.7% of the 72 patients in the INTELENCE arm and in 6.0% of the 67 patients in the placebo arm and grade 3 or 4 elevations in ALT developed in 11.1% of patients in the INTELENCE arm and in 7.5% of patients in the placebo arm. Among co-infected patients, 1.4% of those treated with INTELENCE and 3.0% in the placebo arm discontinued because of liver or biliary system disorders. Standard clinical monitoring of patients with chronic hepatitis is considered adequate.

Adverse Drug Reactions Identified During Postmarketing Experience with INTELENCE

Immune system disorders

Hypersensitivity reactions including DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have been reported and were characterized by rash, constitutional findings, and infrequently organ dysfunction, including hepatic failure (see section 4.4).

Musculoskeletal and connective tissue disorders

Rhabdomyolysis

4.9 Overdose

There are no data with regard to symptomatic overdose with INTELENCE, but it is possible that the most frequent ADRs of INTELENCE, i.e. rash, diarrhoea, nausea, and headache would be the most common symptoms noted.

There is no specific antidote for overdose with INTELENCE. Human experience of overdose with INTELENCE is limited. Treatment of overdose with INTELENCE consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since etravirine is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code: J05AG04.

Mechanism of action

Etravirine is an NNRTI of human immunodeficiency virus type 1 (HIV-1). Etravirine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

Antiviral activity *in vitro*

Etravirine exhibits activity against wild type HIV-1 in T-cell lines and primary cells with median EC₅₀ values ranging from 0.9 to 5.5 nM. Etravirine demonstrates activity against HIV-1 group M (subtypes A, B, C, D, E, F, and G) and HIV-1 group O primary isolates with EC₅₀ values ranging from 0.3 to 1.7 nM and from 11.5 to 21.7 nM, respectively. Although etravirine demonstrates *in vitro* activity against wild type HIV-2 with median EC₅₀ values ranging from 5.7 to 7.2 µM, treatment of HIV-2 infection with etravirine is not recommended in the absence of clinical data. Etravirine retains activity against HIV-1 viral strains resistant to nucleoside reverse transcriptase and/or protease inhibitors. In addition, etravirine demonstrates a fold change (FC) in EC₅₀ ≤ 3 against 60% of 6,171 NNRTI-resistant clinical isolates.

Resistance

Etravirine efficacy in relation to NNRTI resistance at baseline has mainly been analysed with etravirine given in combination with darunavir/ritonavir (DUET-1 and DUET-2). Boosted protease inhibitors, like darunavir/ritonavir, show a higher barrier to resistance compared to other classes of antiretrovirals. The breakpoints for reduced efficacy with etravirine (> 2 etravirine-associated mutations at baseline, see clinical results section) applies when etravirine is given in combination with a boosted protease inhibitor. This breakpoint might be lower in antiretroviral combination therapy not including a boosted protease inhibitor.

In the Phase III trials DUET-1 and DUET-2, mutations that developed most commonly in patients with virologic failure to the INTELENCE containing regimen were V108I, V179F, V179I, Y181C and Y181I, which usually emerged in a background of multiple other NNRTI resistance-associated mutations (RAMs). In all the other trials conducted with INTELENCE in HIV-1 infected patients, the following mutations emerged most commonly: L100I, E138G, V179F, V179I, Y181C and H221Y.

Cross-resistance

Following virologic failure of an etravirine-containing regimen it is not recommended to treat patients with efavirenz and/or nevirapine.

Clinical efficacy and safety

Treatment-experienced adult patients

Pivotal studies

The evidence of efficacy of INTELENCE is based on 48-week data from 2 Phase III trials DUET-1 and DUET-2. These trials were identical in design and similar efficacy for INTELENCE was seen in each trial. The results below are pooled data from the two trials.

Trial characteristics

- Design: randomised (1:1), double-blinded, placebo-controlled.

- Treatment: INTELENCE vs. placebo, in addition to a background regimen including darunavir/ritonavir (DRV/r), investigator-selected N(t)RTIs and optional enfuvirtide (ENF).
- Main inclusion criteria:
 - HIV-1 plasma viral load > 5,000 HIV-1 RNA copies/ml at screening
 - 1 or more NNRTI resistance-associated mutations (RAMs) at screening or from prior genotypic analysis (i.e., archived resistance)
 - 3 or more primary PI mutations at screening
 - on a stable antiretroviral regimen for at least 8 weeks.
- Stratification: Randomisation was stratified by the intended use of ENF in the BR, previous use of darunavir and screening viral load.
- Virologic response was defined as achieving a confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml).

Summary of efficacy results

| Table 3: DUET-1 and DUET-2 pooled 48-week data | | | |
|--|---------------------------------|---------------------------------|--------------------------------------|
| | INTELENCE + BR N = 599 | Placebo + BR N = 604 | Treatment difference (95% CI) |
| <i>Baseline characteristics</i> | | | |
| Median plasma HIV-1 RNA | 4.8 log ₁₀ copies/ml | 4.8 log ₁₀ copies/ml | |
| Median CD4 cell count | 99 x 10 ⁶ cells/l | 109 x 10 ⁶ cells/l | |
| <i>Outcomes</i> | | | |
| Confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml) ^a n (%) | | | |
| Overall | 363 (60.6%) | 240 (39.7%) | 20.9% (15.3%; 26.4%) ^d |
| <i>De novo</i> ENF | 109 (71.2%) | 93 (58.5%) | 12.8% (2.3%; 23.2%) ^f |
| Not <i>de novo</i> ENF | 254 (57.0%) | 147 (33.0%) | 23.9% (17.6%; 30.3%) ^f |
| < 400 HIV-1 RNA copies/ml ^a n (%) | 428 (71.5%) | 286 (47.4%) | 24.1% (18.7%; 29.5%) ^d |
| HIV-1 RNA log ₁₀ mean change from baseline (log ₁₀ copies/ml) ^b | -2.25 | -1.49 | -0.6 (-0.8; -0.5) ^c |
| CD4 cell count mean change from baseline (x 10 ⁶ /l) ^b | +98.2 | +72.9 | 24.4 (10.4; 38.5) ^c |
| Any AIDS defining illness and/or death n (%) | 35 (5.8%) | 59 (9.8%) | -3.9% (-6.9%; -0.9%) ^e |

- ^a Imputations according to the TLOVR algorithm (TLOVR = Time to Loss of Virologic Response).
- ^b Non-completer is failure (NC = F) imputation.
- ^c Treatment differences are based on Least Square Means from an ANCOVA model including the stratification factors. P-value < 0.0001 for mean decrease in HIV-1 RNA; P-value = 0.0006 for mean change in CD4 cell count.
- ^d Confidence interval around observed difference of response rates; P-value < 0.0001 from logistic regression model, including stratification factors.
- ^e Confidence interval around observed difference of response rates; P-value = 0.0408.
- ^f Confidence interval around observed difference of response rates; P-value from CMH test controlling for stratification factors = 0.0199 for *de novo*, and < 0.0001 for not *de novo*.

Since there was a significant interaction effect between treatment and ENF, the primary analysis was done for 2 ENF strata (patients reusing or not using ENF versus patients using ENF *de novo*). The week 48 results from the pooled analysis of DUET-1 and DUET-2 demonstrated that the INTELENCE arm was superior to the placebo arm irrespective of whether ENF was used *de novo* ($p = 0.0199$) or not ($p < 0.0001$). Results of this analysis (week 48 data) by ENF stratum are shown in table 3.

Significantly fewer patients in the INTELENCE arm reached a clinical endpoint (AIDS-defining illness and/or death) as compared to the placebo arm ($p = 0.0408$).

A subgroup analysis of the virologic response (defined as a viral load < 50 HIV-1 RNA copies/ml) at week 48 by baseline viral load and baseline CD4 count (pooled DUET data) is presented in table 4.

| Table 4: DUET-1 and DUET-2 pooled data | | |
|---|---|-------------------------|
| Subgroups | Proportion of subjects with HIV-1 RNA < 50 copies/ml at week 48 | |
| | INTELENCE + BR N = 599 | Placebo + BR N = 604 |
| Baseline HIV-1 RNA | | |
| < 30,000 copies/ml | 75.8% | 55.7% |
| ≥ 30,000 and < 100,000 copies/ml | 61.2% | 38.5% |
| ≥ 100,000 copies/ml | 49.1% | 28.1% |
| Baseline CD4 count (x 10 ⁶ /l) | | |
| < 50 | 45.1% | 21.5% |
| ≥ 50 and < 200 | 65.4% | 47.6% |
| ≥ 200 and < 350 | 73.9% | 52.0% |
| ≥ 350 | 72.4% | 50.8% |

Note: Imputations according to the TLOVR algorithm (TLOVR = Time to Loss of Virologic Response)

Baseline genotype or phenotype and virologic outcome analyses

In DUET-1 and DUET-2, the presence at baseline of 3 or more of the following mutations: V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A and G190S, (INTELENCE RAMs) was associated with a decreased virologic response to INTELENCE (see table 5). These individual mutations occurred in the presence of other NNRTI RAMs. V179F was never present without Y181C.

Conclusions regarding the relevance of particular mutations or mutational patterns are subject to change with additional data, and it is recommended to always consult current interpretation systems for analysing resistance test results.

| Table 5: Proportion of subjects with < 50 HIV-1 RNA copies/ml at week 48 by baseline number of INTELENCE RAMs in the non-viral failure excluded population of pooled DUET-1 and DUET-2 trials | | |
|---|----------------------------|--------------------|
| Baseline number of INTELENCE RAMs* | Etravirine arms N = 549 | |
| | Reused/not used ENF | <i>De novo</i> ENF |
| All ranges | 63.3% (254/401) | 78.4% (109/139) |
| 0 | 74.1% (117/158) | 91.3% (42/46) |
| 1 | 61.3% (73/119) | 80.4% (41/51) |
| 2 | 64.1% (41/64) | 66.7% (18/27) |
| ≥ 3 | 38.3% (23/60) | 53.3% (8/15) |
| | Placebo arms N = 569 | |
| All ranges | 37.1% (147/396) | 64.1% (93/145) |

* INTELENCE RAMs = V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S

Note: all patients in the DUET trials received a background regimen consisting of darunavir/rtv, investigator-selected NRTIs and optional enfuvirtide.

The presence of K103N alone, which was the most prevalent NNRTI mutation in DUET-1 and DUET-2 at baseline, was not identified as a mutation associated with resistance to INTELENCE. Furthermore, the presence of this mutation alone did not affect the response in the INTELENCE arm. Additional data is required to conclude on the influence of K103N when associated with other NNRTIs mutations.

Data from the DUET studies suggest that baseline fold change (FC) in EC₅₀ to etravirine was a predictive factor of virologic outcome, with gradually decreasing responses observed above FC 3 and FC 13.

FC subgroups are based on the select patient populations in DUET-1 and DUET-2 and are not meant to represent definitive clinical susceptibility breakpoints for INTELENCE.

Exploratory head to head comparison with protease inhibitor in protease inhibitor naïve patients (trial TMC125-C227)

TMC125-C227 was an exploratory, randomised, active-controlled open-label trial, which investigated the efficacy and safety of INTELENCE in a treatment regimen, which is not approved under the current indication. In the TMC125-C227 study, INTELENCE (N = 59) was administered with 2 investigator-selected NRTIs (i.e. without a ritonavir-boosted PI) and compared to an investigator-selected combination of a PI with 2 NRTIs (N = 57). The trial population included PI-naïve, NNRTI-experienced patients with evidence of NNRTI resistance.

At week 12, virologic response was greater in the control-PI arm ($-2.2 \log_{10}$ copies/ml from baseline; $n = 53$) compared to the INTELENCE arm ($-1.4 \log_{10}$ copies/ml from baseline; $n = 40$). This difference between treatment arms was statistically significant.

Based on these trial results, INTELENCE is not recommended for use in combination with N(t)RTIs only in patients who have experienced virological failure on an NNRTI- and N(t)RTI-containing regimen.

Pregnancy and postpartum

INTELENCE (200 mg b.i.d.), evaluated in combination with other antiretroviral medicinal products in a study of 15 pregnant women during the second and third trimesters of pregnancy and postpartum, demonstrated that exposure to total etravirine was generally higher during pregnancy compared with postpartum, and less so for unbound etravirine exposure (see section 5.2). There were no new clinically relevant safety findings in the mothers or in the newborns in this trial.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of etravirine have been evaluated in adult healthy subjects and in adult treatment-experienced HIV-1 infected patients. Exposure to etravirine was lower (35-50%) in HIV-1 infected patients than in healthy subjects.

Table 6: Population pharmacokinetic estimates of etravirine 200 mg b.i.d. in HIV-1-infected adult subjects (integrated data from Phase III trials at week 48)*

| Parameter | Etravirine 200 mg b.i.d. N = 575 |
|--|-------------------------------------|
| AUC _{12h} (ng•h/ml) | |
| Geometric Mean \pm Standard Deviation | 4522 \pm 4710 |
| Median (Range) | 4380 (458 - 59084) |
| C _{0h} (ng/ml) | |
| Geometric Mean \pm Standard Deviation | 297 \pm 391 |
| Median (Range) | 298 (2 - 4852) |
| * All HIV-1-infected subjects enrolled in Phase III clinical trials received darunavir/ritonavir 600/100 mg b.i.d. as part of their background regimen. Therefore, the pharmacokinetic parameter estimates shown in the table account for reductions in the pharmacokinetic parameters of etravirine due to co-administration of INTELENCE with darunavir/ritonavir. | |
| Note: The median protein binding adjusted EC50 for MT4 cells infected with HIV-1/IIIB in vitro = 4 ng/ml. | |

Absorption

An intravenous formulation of etravirine is unavailable, thus, the absolute bioavailability of INTELENCE is unknown. After oral administration with food, the maximum plasma concentration of etravirine is generally achieved within 4 hours. In healthy subjects, the absorption of etravirine is not affected by co-administration of oral ranitidine or omeprazole, drugs that are known to increase gastric pH.

Effect of food on absorption

The systemic exposure (AUC) to etravirine was decreased by about 50% when INTELENCE was administered under fasting conditions, as compared to administration following a meal. Therefore, INTELENCE should be taken following a meal.

Distribution

Etravirine is approximately 99.9% bound to plasma proteins, primarily to albumin (99.6%) and α 1-acid glycoprotein (97.66%-99.02%) *in vitro*. The distribution of etravirine into compartments other than plasma (e.g, cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Metabolism

In vitro experiments with human liver microsomes (HLMs) indicate that etravirine primarily undergoes oxidative metabolism by the hepatic cytochrome P450 (CYP) 3A system and, to a lesser extent, by the CYP2C family followed by glucuronidation.

Elimination

After administration of a radiolabeled ^{14}C -etravirine dose, 93.7% and 1.2% of the administered dose of ^{14}C -etravirine could be retrieved in faeces and urine, respectively. Unchanged etravirine accounted for 81.2% to 86.4% of the administered dose in feces.

Unchanged etravirine in faeces is likely to be unabsorbed drug. Unchanged etravirine was not detected in urine. The terminal elimination half-life of etravirine was approximately 30-40 hours.

Additional information on special populations

Children and adolescents

Treatment with INTELENCE in Israel is not approved in children and adolescents

Elderly

Population pharmacokinetic analysis in HIV infected patients showed that etravirine pharmacokinetics are not considerably different in the age range (18 to 77 years) evaluated, with 6 subjects aged 65 years or older (see section 4.2 and 4.4).

Gender

No significant pharmacokinetic differences have been observed between males and females. A limited number of females were included in the studies.

Race

Population pharmacokinetic analysis of etravirine in HIV infected patients indicated no apparent difference in the exposure to etravirine between Caucasian, Hispanic and Black subjects. The pharmacokinetics in other races have not been sufficiently evaluated.

Hepatic impairment

Etravirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild (Child-Pugh score A) hepatic impairment to 8 matched controls and 8 patients with moderate (Child-Pugh score B) hepatic impairment to 8 matched controls, the multiple dose pharmacokinetic disposition of etravirine was not altered in patients with mild to moderate hepatic impairment.

However, unbound concentrations have not been assessed. Increased unbound exposure could be expected. No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. INTELENCE has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and is therefore not recommended (see sections 4.2 and 4.4).

Hepatitis B and/or hepatitis C virus co-infection

Population pharmacokinetic analysis of the DUET-1 and DUET-2 trials showed reduced clearance (potentially leading to increased exposure and alteration of the safety profile) for INTELENCE in HIV-1 infected patients with hepatitis B and/or hepatitis C virus co-infection. In view of the limited data available in hepatitis B and/or C co-infected patients, particular caution should be paid when INTELENCE is used in these patients (see sections 4.4 and 4.8).

Renal impairment

The pharmacokinetics of etravirine have not been studied in patients with renal insufficiency. Results from a mass balance study with radioactive ¹⁴C-etravirine showed that <1.2% of the administered dose of etravirine is excreted in the urine. No unchanged drug was detected in urine so the impact of renal impairment on etravirine elimination is expected to be minimal. As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see sections 4.2).

Pregnancy and postpartum

Study TMC114HIV3015 evaluated etravirine 200 mg b.i.d. in combination with other antiretroviral medicinal products in 15 pregnant women during the second and third trimesters of pregnancy and postpartum. The total etravirine exposure after intake of etravirine 200 mg b.i.d. as part of an antiretroviral regimen was generally higher during pregnancy compared with postpartum (see Table 9). The differences were less pronounced for unbound etravirine exposure. In women receiving etravirine 200 mg b.i.d., higher mean values for C_{max} , AUC_{12h} and C_{min} were observed during pregnancy compared to postpartum. During the 2nd and 3rd trimester of pregnancy mean values of these parameters were comparable.

| Table 9: Pharmacokinetic results of total etravirine after administration of etravirine 200 mg b.i.d. as part of an antiretroviral regimen, during the 2nd trimester of pregnancy, the 3rd trimester of pregnancy, and postpartum. | | | |
|---|--|--|--|
| Pharmacokinetics of etravirine (mean \pm SD, median) | etravirine 200 mg b.i.d. postpartum | etravirine 200 mg b.i.d. 2nd trimester | etravirine 200 mg b.i.d. 3rd trimester |
| N | 10 | 13 | 10 ^a |
| C_{min} , ng/mL | 269 \pm 182 284 | 383 \pm 210 346 | 349 \pm 103 371 |
| C_{max} , ng/mL | 569 \pm 261 528 | 774 \pm 300 828 | 785 \pm 238 694 |
| AUC_{12h} , h*ng/mL | 5004 \pm 2521 5246 | 6617 \pm 2766 6836 | 6846 \pm 1482 6028 |

^a n = 9 for AUC_{12h}

Each subject served as her own control, and with an intra-individual comparison, the total etravirine C_{min} , C_{max} and AUC_{12h} values were 1.2-, 1.4- and 1.4-fold higher, respectively, during the 2nd trimester of pregnancy as compared to postpartum, and 1.1-, 1.4- and 1.2-fold higher, respectively, based during the 3rd trimester of pregnancy as compared to postpartum.

5.3 Preclinical safety data

Animal toxicology studies have been conducted with etravirine in mice, rats, rabbits and dogs. In mice, the key target organs identified were the liver and the coagulation system. Haemorrhagic cardiomyopathy was only observed in male mice and was considered to be secondary to severe coagulopathy mediated via the vitamin K pathway. In the rat, the key target organs identified were the liver, the thyroid and the coagulation system. Exposure in mice was equivalent to human exposure while in rats it was below the clinical exposure at the recommended dose. In the dog, changes were observed in the liver and gall bladder at exposures approximately 8-fold higher than human exposure observed at the recommended dose (200 mg b.i.d.).

In a study conducted in rats, there were no effects on mating or fertility at exposure levels equivalent to those in humans at the clinically recommended dose. There was no teratogenicity with etravirine in rats and rabbits at exposures equivalent to those observed in humans at the recommended clinical dose. Etravirine had no effect on offspring development during lactation or post weaning at maternal exposures equivalent to those observed at the recommended clinical dose.

Etravirine was not carcinogenic in rats and in male mice. An increase in the incidences of hepatocellular adenomas and carcinomas were observed in female mice. The observed hepatocellular findings in female mice are generally considered to be rodent specific, associated with liver enzyme induction, and of limited relevance to humans. At the highest tested doses, the systemic exposures (based on AUC) to etravirine were 0.6-fold (mice) and between 0.2- and 0.7-fold (rats), relative to those observed in humans at the recommended therapeutic dose (200 mg b.i.d.).

In vitro and *in vivo* studies with etravirine revealed no evidence of a mutagenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

INTELENCE™ 100 mg tablets:

Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Croscarmellose sodium
Magnesium stearate
Lactose monohydrate

INTELENCE™ 200 mg tablets:

Hypromellose
Microcrystalline cellulose
Colloidal anhydrous silica
Croscarmellose sodium
Magnesium stearate
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original bottle. Keep the bottle tightly closed in order to protect from moisture. Do not remove the desiccant pouches.

After first opening-use up to 2 months.

6.5 Nature and contents of container

INTELENCE 100 mg and 200 mg tablets are provided in a high density polyethylene (HDPE) plastic bottle containing 3 desiccant pouches, fitted with a polypropylene (PP) child resistant closure.

| Tablet strength | Presentation (tablets/bottle) |
|-----------------|-------------------------------|
| 100 mg | 120 |
| 200 mg | 60 |

6.6 Special precautions for disposal and other handling

No special requirements.

Manufacturer: Janssen Cilag S.p.A., Latina, Italy

Registration holder: J-C Health Care Ltd. Kibbutz Shefayim, 60990

The format of this leaflet was determined by the ministry of health and its content was checked and approved
