הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

אושר – 5.16

תאריך: 22.05.2016

שם תכשיר באנגלית ומספר הרישום: Edurant Tablet 148.57.33585.00

שם בעל הרישום: J-C Health Care Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	טקסט נוכחי	פרק בעלון
5.2 Skin and Hypersensitivity Reactions Severe skin and hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase 3 clinical trials, treatment-related rashes with at least Grade 2 severity were reported in 3% of subjects receiving EDURANT. No grade 4 rash was reported. Overall, most rashes were Grade 1 or 2 and occurred in the first four to six weeks of therapy [see Adverse Reactions (6 and 6.2)]. Discontinue EDURANT immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated. **5.3 Depressive Disorders** ~~The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with EDURANT. During the Phase 3 trials (N = 1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among EDURANT (n = 686) or efavirenz (n = 682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both EDURANT and efavirenz. The~~	**5.3 Depressive Disorders** The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with EDURANT. During the Phase 3 trials (N = 1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among EDURANT (n = 686) or efavirenz (n = 682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both EDURANT and efavirenz. The incidence of discontinuation due to depressive disorders among EDURANT or efavirenz was 1% in each arm. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the EDURANT arm. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to EDURANT, and if so, to	**WARNINGS AND PRECAUTIONS**

~~incidence of discontinuation due to depressive disorders among EDURANT or efavirenz was 1% in each arm. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the EDURANT arm. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to EDURANT, and if so, to determine whether the risks of continued therapy outweigh the benefits~~. The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with EDURANT. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to EDURANT, and if so, to determine whether the risks of continued therapy outweigh the benefits. During the Phase 3 trials in adults (N = 1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among EDURANT (n = 686) or efavirenz (n = 682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both EDURANT and efavirenz. The incidence of discontinuation due to depressive disorders among EDURANT or efavirenz was 1% in each arm. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the EDURANT arm. During the Phase 2 trial in pediatric subjects 12 to less than 18 years of age (N = 36) receiving EDURANT through 48 weeks, the incidence of depressive disorders (regardless of causality, severity) was 19.4% (7/36). Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 5.6% (2/36). None of the subjects discontinued due to depressive disorders. Suicidal ideation and suicide attempt were reported in 1 subject. **5.5 Fat Redistribution** Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. ~~A higher risk of lipodystrophy has been associated with individual factors such as older age and with drug-related factors such as longer~~	determine whether the risks of continued therapy outweigh the benefits. **5.5 Fat Redistribution** Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established. 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	

~~duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.~~		
The following adverse drug reaction (ADR) is discussed in greater detail in other sections of the package insert: Skin and Hypersensitivity Reactions [*see Warnings and Precautions (5.2)]* Depressive Disorders [*see Warnings and Precautions (5.3)*] Hepatotoxicity [*see Warnings and Precautions (5.4*)] *Adrenal Function* ~~In the pooled Phase 3 trials, at Week 96, there was an overall mean change from baseline in basal cortisol of -19.1 (-30.85; -7.37) nmol/L in the EDURANT group and of -0.6 (-13.29; 12.17) nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT group (+18.4 ± 8.36 nmol/L) than in the efavirenz group (+54.1 ± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency.~~ In the pooled Phase 3 trials, at Week 96, there was an overall mean change from baseline in basal cortisol of -0.69 (-1.12, 0.27) micrograms/dL in the EDURANT group and of -0.02 (-0.48, 0.44) micrograms/dL in the efavirenz group. In the EDURANT group, 43/588 (7.3%) of subjects with a normal 250 micrograms ACTH stimulation test at baseline developed an abnormal 250 micrograms ACTH stimulation test (peak cortisol level < 18.1 micrograms/dL) during the trial compared to 18/561 (3.2%) in the efavirenz group. Of the subjects who developed an abnormal 250 micrograms ACTH stimulation test during the trial, fourteen subjects in the EDURANT group and nine subjects in the efavirenz group had an abnormal 250 micrograms ACTH stimulation test at Week 96. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the higher abnormal rate of 250 micrograms ACTH stimulation tests in the EDURANT group is not known.	The following adverse drug reaction (ADR) is discussed in greater detail in other sections of the package insert: Depressive Disorders [*see Warnings and Precautions (5.3)*] Hepatotoxicity [*see Warnings and Precautions (5.4*)] *Adrenal Function* In the pooled Phase 3 trials, at Week 96, there was an overall mean change from baseline in basal cortisol of -19.1 (-30.85; -7.37) nmol/L in the EDURANT group and of -0.6 (-13.29; 12.17) nmol/L in the efavirenz group. At Week 96, the mean change from baseline in ACTH-stimulated cortisol levels was lower in the EDURANT group (+18.4 ± 8.36 nmol/L) than in the efavirenz group (+54.1 ± 7.24 nmol/L). Mean values for both basal and ACTH-stimulated cortisol values at Week 96 were within the normal range. Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. *Lipodystrophy* CART 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 dorsocervical fat accumulation (buffalo	**ADVERSE REACTIONS**

~~*Lipodystrophy*~~ ~~CART 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 dorsocervical fat accumulation (buffalo hump) .~~ **6.1 Postmarketing Experience** Adverse reactions have been identified during post-marketing in patients receiving a rilpivirine containing regimen. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Renal and Genitourinary Disorders*: nephrotic syndrome *Skin and Subcutaneous Tissue Disorders:* Severe skin and hypersensitivity reactions including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)	hump) . **6.1 Postmarketing Experience** Adverse reactions have been identified during post-marketing in patients receiving a rilpivirine containing regimen. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Renal and Genitourinary Disorders*: nephrotic syndrome	
Antacids: Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate) Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (reduced absorption due to gastric pH increase) The combination of EDURANT and antacids should be used with particular caution. Antacids should only be administered either at least 2 hours before or at least 4 hours after EDURANT. Rilpivirine did not have a clinically significant effect on the pharmacokinetics of digoxin or metformin. ~~Metformin (ANTIDIABETICS) Not studied. It may not be excluded that rilpivirine will give rise to increased exposure of metformin (inhibition of the active renal secretion of metformin). Careful patient monitoring is advised when starting or ending concomitant treatment.~~	Rilpivirine did not have a clinically significant effect on the pharmacokinetics of digoxin . Metformin (ANTIDIABETICS)- Not studied. It may not be excluded that rilpivirine will give rise to increased exposure of metformin (inhibition of the active renal secretion of metformin). Careful patient monitoring is advised when starting or ending concomitant treatment.	**Interactions**
~~Safety and effectiveness in pediatric patients have not been established.~~ The safety, efficacy and pharmacokinetics of	Safety and effectiveness in pediatric patients have not been established.	**USE IN SPECIFIC POPULATIONS**

EDURANT were evaluated in a single arm, open-label, Phase 2 trial that enrolled 36 antiretroviral treatment-naïve, HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg . Safety and effectiveness in pediatric patients less than 12 years of age have not been established. In Israel Edurat is approved for use only in adult patient.		
Patients should be informed that skin reactions ranging from mild to severe, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported with rilpivirine-containing regimens. Instruct patients to immediately stop taking EDURANT tablets and seek medical attention if they develop a rash associated with any of the following symptoms: fever, blisters, mucosal involvement, eye inflammation (conjunctivitis), severe allergic reaction causing a swelling of the face, eyes, lips, mouth, tongue or throat, which may lead to difficulty swallowing or breathing, and any signs and symptoms of liver problems as it may be a sign of a more serious reaction. Patients should understand that if severe rash occurs, they will be closely monitored, laboratory tests will be performed and appropriate therapy will be initiated.		**PATIENT COUNSELING INFORMATION**

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב,אפור וכחול (בהתאם לרפרנס ממנו נלקחה ההחמרה).
שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך...22.05.2016

הודעה על החמרה (מידע בטיחות) בעלון לצרכן

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ההחמרות המבוקשות		
פרק בעלון	טקסט נוכחי	טקסט חדש

אזהרות מיוחדות הנוגעות בשימוש בתרופה:	• אדרונאט אינו מיועד לשימוש בילדים או מתבגרים כיוון שאין מספיק מידע על השימוש בחולים מתחת לגיל 18 שנים.	• אדרונאט אינו מיועד לשימוש בילדים או מתבגרים ~~כיוון שאין מספיק מידע על השימוש בחולים~~ מתחת לגיל 18 שנים
אם אתה לוקח , או אם לקחת לאחרונה ,תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח	• מטפורמין (לטיפול בסכרת)	○ ~~מטפורמין (לטיפול בסכרת)~~
תופעות לוואי	אדוראנט עלול לגרום לתופעות הלוואי החמורות הבאות: -שינויים בשומן בגוף עלולים להתרחש באנשים הנוטלים תרופות לטיפול ב-**HIV** . שינויים אלו יכולים לכלול עליה בכמות השומן בגב העליון ובצוואר (**"buffalo humps"**) , חזה ובאיזור מרכז הגוף . ייתכן גם אובדן שומן מהרגליים, זרועות ופנים. תופעות לוואי המופיעות לעיתים קרובות: תופעות המופיעות ביותר ממשתמש אחד מתוך 10 : עלייה בכולסטרול ו/או באינזים הלבלב הנקרא עמילז, בדם שינוי בתוצאות בדיקות תפקודי כבד כאב ראש בחילה סחרחורת תופעות המופיעות ביותר בפחות ממשתמש אחד מתוך 10 ספירה נמוכה של תאי דם לבנים ו/או טסיות, ירידה בהמוגלובין בדם, עלייה בטריגליצרידים בדם, עליה בליפאז ו/או בילירובין בדם.	אדוראנט עלול לגרום לתופעות הלוואי החמורות הבאות: -פריחה עורית ותגובה אלרגית חמורות. פריחה עורית הינה תופעת לוואי שכיחה של אדורנט. פריחה עורית עלולה להיות חמורה ועלולה להזדקק לטיפול בבית חולים. יש להודיע לרופא באופן מיידי עם יש לך פריחה. אם מתפתחת לך פריחה עם אחד מהתסמינים הבאים, יש להפסיק נטילת אודורנט לפנות לעזרה רפואית מיידית: חום, פצעים על העור, פצעים בפה, התנפחות של הפנים, שפתיים, פה לשון או גרון, קושי בנשימה או בבליעה, כאב בחלק הימני של איזור הבטן, שתן בצבע כהה. -שינויים בשומן בגוף עלולים להתרחש באנשים הנוטלים תרופות לטיפול ב-**HIV** . שינויים אלו יכולים לכלול עליה בכמות השומן בגב העליון ובצוואר (**"buffalo humps"**) , חזה ובאיזור מרכז הגוף . ייתכן גם אובדן שומן מהרגליים, זרועות ופנים. הסיבה המדויקת וההשפעות הבריאותיות ארוכות הטווח של בעיות אלה אינן ידועות. תופעות לוואי המופיעות לעיתים קרובות: תופעות המופיעות ביותר ממשתמש אחד מתוך 10 : עלייה בכולסטרול ו/או באינזים הלבלב הנקרא עמילז, בדם שינוי בתוצאות בדיקות תפקודי כבד כאב ראש דיכאון, מצב רוח דיכאוני קושי להירדם (אינסומניה) פריחה בחילה סחרחורת

	ירידה בתאבון דיכאון, מצב רוח דיכאוני חלומות לא רגיליים, קושי להירדם (אינסומניה), הפרעות בשינה נמנום כאב בטן, הקאות, חוסר נוחות בבטן, יובש בפה פריחה עייפות	תופעות המופיעות ביותר בפחות ממשתמש אחד מתוך 10 ספירה נמוכה של תאי דם לבנים ו/או טסיות, ירידה בהמוגלובין בדם, עלייה בטריגליצרידים בדם, עליה בליפאז ו/או בילירובין בדם. ירידה בתאבון ~~דיכאון, מצב רוח דיכאוני~~ חלומות לא רגיליים~~, קושי להירדם~~ ~~(אינסומניה),~~ הפרעות בשינה נמנום כאב בטן, הקאות, חוסר נוחות בבטן, יובש בפה ~~פריחה~~ עייפות

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