J-C Health Care Ltd.

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10-2025

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: רזולסטה, Rezolsta

חברת J-C Health Care Ltd מבקשת להודיעכם כי העלון לרופא של התכשיר שבנדון התעדכן ב 10-2025.

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן בטקסט ~~כחול עם קו חוצה~~, טקסט המהווה החמרה מודגש ברקע צהוב),אך קיימים עדכונים נוספים.

ההתוויות המאושרות לתכשיר בישראל:

REZOLSTA is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV 1) infection in treatment-naïve and treatment-experienced adults with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).
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מרכיב פעיל:

Darunavir (as ethanolate) 800mg; Cobicistat 150 mg

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug.

כמו כן, מצורף לפרסום זה וניתן לקבל העתק מודפס שלו באמצעות פנייה לבעל הרישום: J-C Health Care Ltd, קיבוץ שפיים, 6099000, טל': 09-9591111.

בברכה,

יעל לפידות מללי
רוקחת ממונה

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העדכון בעלון לרופא הינו:

4.2 Posology and method of administration

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Paediatric population

~~The safety and efficacy of REZOLSTA in paediatric patients aged 3 to 11 years, or weighing < 40 kg. have not been established, no data are available. Rezolsta is not indicated for paediatric patients aged 12 to 17 years (see sections 4.4 and 5.3). REZOLSTA should not be used in paediatric patients below 3 years of age because of safety concerns (see sections 4.4 and 5.3).~~Rezolsta is not indicated in children and adolescents below 18 years.
REZOLSTA should not be used in paediatric patients below 3 years of age because of safety concerns (see section 5.3).

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4.4 Special warnings and precautions for use

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Pregnancy

Treatment with darunavir/cobicistat 800/150 mg during the second and third trimester has been shown to result in low darunavir exposure, with a reduction of around 90% in C_{min} levels (see section 5.2). Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in darunavir exposure may result in virological failure and an increased risk of mother to child transmission of HIV infection. Therefore, this combination~~therapy with REZOLSTA~~ should not be initiated during pregnancy, and women who become pregnant during therapy with REZOLSTA should be switched to an alternative regimen (see sections 4.2 and 4.6). Darunavir given with low dose ritonavir may be considered as an alternative.

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Hepatotoxicity

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Appropriate laboratory testing should be conducted prior to initiating therapy with REZOLSTA and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of ~~REZOLSTA~~ treatment.

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly)~~ in patients using REZOLSTA,~~ interruption or discontinuation of treatment should be considered promptly.

Patients with coexisting conditions

Hepatic impairment

The safety and efficacy of ~~REZOLSTA,~~ darunavir~~,~~ and/or cobicistat have not been established in patients with severe underlying liver disorders. REZOLSTA is, therefore, contraindicated in patients with severe hepatic impairment. Due to an increase in the unbound darunavir plasma concentrations, REZOLSTA should be used with caution in patients with mild or moderate hepatic impairment (see sections 4.2, 4.3 and 5.2).

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Paediatric population

~~REZOLSTA is not recommended for use in paediatric patients (3 to 17 years of age). REZOLSTA should not be used in paediatric patients below 3 years of age (see sections 4.2 and 5.3).~~Rezolsta is not indicated in children and adolescents below 18 years.
REZOLSTA should not be used in paediatric patients below 3 years of age (see section 5.3).

Excipients

REZOLSTA contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

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4.5 Interaction with other medicinal products and other forms of interaction

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Interaction table

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The below list of examples of drug drug ~~-~~interactions in Table 1 is not comprehensive and therefore the label of each drug that is co-administered with REZOLSTA should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Table 1: Interactions and dose recommendations with other medicinal products~~INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS~~		
Medicinal product examples by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
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4.6 Fertility, pregnancy and lactation

Pregnancy

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Treatment with darunavir/cobicistat 800/150 mg during pregnancy results in low darunavir exposure (see section 5.2), which may be associated with an increased risk of treatment failure and an increased risk of HIV transmission to the child. ~~Therapy with REZOLSTA~~ Therefore, this combination should not be initiated during pregnancy, and women who become pregnant during therapy with REZOLSTA should be switched to an alternative regimen (see sections 4.2 and 4.4).

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4.8 Undesirable effects

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Tabulated list of adverse reactions

Adverse reactions are listed by system organ class (SOC) and frequency category in Table 2. Within each frequency category, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and not known (frequency cannot be estimated from the available data).

~~Adverse reactions with darunavir/cobicistat in adult patients~~

Table 2 Adverse reactions with darunavir/cobicistat in adult patients	
MedDRA system organ class Frequency category	Adverse reaction
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Paediatric population

~~The safety and efficacy of REZOLSTA in paediatric patients aged 3 to 11 years, or weighing < 40 kg, have not been established, no data are available. Rezolsta is not indicated for paediatric patients aged 12 to 17 years (see sections 4.4 and 5.3).~~ Rezolsta is not indicated in children and adolescents below 18 years.

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4.9 Overdose

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There is no specific antidote for overdose with REZOLSTA. Treatment of overdose ~~with REZOLSTA~~ consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Resistance

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Low rates of developing resistant HIV-1 virus were observed in ART-naïve patients who are treated for the first time with REZOLSTA or darunavir/ritonavir 800/100 mg once daily in combination with other ART, and in ART-experienced patients with no darunavir RAMs receiving REZOLSTA or darunavir/ritonavir 800/100 mg once daily in combination with other ART. ~~The t~~Table 3 below shows the development of HIV-1 protease mutations and loss of susceptibility to HIV PIs in virologic failures at endpoint in the GS-US-216-130, ARTEMIS and ODIN trials.

Table 3

	GS-US-216-130[a]		ARTEMIS[b]	ODIN[b]	
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Description of clinical studies of REZOLSTA in adults

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HIV-1 infected patients who were eligible for this trial had a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA ≥ 1,000 copies/mL. ~~The t~~Table 4 below shows the efficacy data of the 48 week analyses from the GS-US-216-130 trial:

Table 4

	GS-US-216-130		
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Efficacy of darunavir/cobicistat fixed-dose combination 800/150 mg once daily in ART-naïve patients

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HIV-1 infected patients who were eligible for this trial had a plasma HIV-1 RNA ≥ 1,000 copies/mL. ~~The t~~Table 5 below shows the 48-week efficacy data of the darunavir/cobicistat arm of the TMC114FD2HTX3001 trial:

Table 5

	TMC114FD2HTX3001 (darunavir/cobicistat arm)
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Description of clinical studies of darunavir/ritonavir in adults

Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-naïve patients

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The table 6 below shows the efficacy data of the 48 week and 96 week analyses from the ARTEMIS trial:

Table 6						
ARTEMIS						
	Week 48[a]			Week 96[b]		
…						

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Efficacy of darunavir 800 mg once daily co-administered with 100 mg ritonavir once daily in ART-experienced patients

ODIN is a Phase III, randomised, open-label trial comparing darunavir/ritonavir 800/100 mg once daily versus darunavir/ritonavir 600/100 mg twice daily in ART-experienced HIV-1 infected patients with screening genotype resistance testing showing no darunavir RAMs (i.e. V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V) and a screening HIV-1 RNA > 1,000 copies/mL. Efficacy analysis is based on 48 weeks of treatment (see Table 7 below). Both arms used an optimised background regimen (OBR) of ≥ 2 NRTIs.

Table 7	
ODIN	
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5.2 Pharmacokinetic properties

Darunavir exposure was shown to be comparable in a bioavailability trial between REZOLSTA and darunavir/ritonavir 800/100 mg q.d. at steady-state and fed conditions in healthy subjects.
The bioequivalence between REZOLSTA and darunavir/cobicistat ~~800/150 mg~~ co-administered as single agents was established for 800/150 mg under fed and fasted conditions in healthy subjects.
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Special populations

Paediatric population

~~The pharmacokinetics of REZOLSTA in paediatric patients aged 3 to 11 years, or weighing < 40 kg, have not been established, no data are available. REZOLSTA is not indicated in paediatric patients aged 12 to 17 years.~~ Rezolsta is not indicated in children and adolescents below 18 years.

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Hepatitis B and/or hepatitis C virus co-infection

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Pregnancy and postpartum

Treatment with REZOLSTA during pregnancy results in low darunavir exposure. In women receiving REZOLSTA during the second trimester of pregnancy, mean intra-individual values for total darunavir C_{max}, AUC_{24h} and C_{min} were 49%, 56% and 92% lower, respectively, as compared with postpartum; during the third trimester of pregnancy, total darunavir C_{max}, AUC_{24h} and C_{min} values were 37%, 50% and 89% lower, respectively, as compared with postpartum. The unbound fraction was also substantially reduced, including around 90% reductions of C_{min} levels. The main cause of these low exposures is a marked reduction in cobicistat exposure as a consequence of pregnancy-associated enzyme induction (see Table 8 below).

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Table 8 Pharmacokinetic results of total darunavir after administration of darunavir/cobicistat 800/150 mg once daily as part of an antiretroviral regimen, during the second trimester of pregnancy, the third trimester of pregnancy, and postpartum			
Pharmacokinetics of total darunavir (mean ± SD)	**Second trimester of pregnancy N=7**	**Third trimester of pregnancy N=6**	**Postpartum (6-12 weeks) N=6**
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