הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

תאריך : 25-May-2014

שם תכשיר באנגלית: Norvir 100 mg Tablets

מספר הרישום: 148-06-33504-00

שם בעל הרישום : AbbVie Biopharmaceuticals Ltd.

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
Contraindications	החמרות אלה התווספו עקב אימוץ העלון האירופאי כלשונו.	Ritonavir should not be given as a pharmacokinetic enhancer or as an antiretroviral agent to patients with decompensated liver disease.

Medicinal Product Class	Medicinal Products within Class	Rationale
Concomitant medicinal product levels increased or decreased		
Analgesics	Pethidine, piroxicam, propoxyphne	Increased plasma concentrations of norpethidine, piroxicam and propoxyphene. Thereby, increasing the risk of serious respiratory depression or haematologic abnormalities, or other serious adverse effects from these agents.
Antiarrthymics	Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, quinidine. Thereby, increasing the risk of arrhythmias or other serious adverse effects from these agents.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antihistamines	Astemizole, terfenadine	Increased plasma concentrations of astemizole and terfenadine. Thereby, increasing the risk of serious arrhythmias from these agents.
Antimycobacterial	Rifabutin	Concomitant use of ritonavir dosed as an antiretroviral agent (600 mg twice daily) and rifabutin due to an increase of rifabutin serum

		concentrations and risk of adverse reactions including uveitis (see section 4.4). Recommendations regarding use of ritonavir dosed as a pharmacokinetic enhancer with rifabutin are noted in section 4.5
Antipsychotics/ Neuroleptics	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious haematologic abnormalities, or other serious adverse effects from these agents. Taking Pimozide and Norvir - Potential for cardiac arrhythmias.
	Quetiapine	Increased plasma concentrations of quetiapine which may lead to coma. The concomitant administration with quetiapine is contraindicated (see section 4.5).
PDE5 inhibitor	Avanafil	Increased plasma concentrations of avanafil (see section 4.4. and 4.5).
	Vardenafil	Increased plasma concentrations of vardenafil (see section 4.4. and 4.5).
Sedatives/hypnotics	Clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam	Increased plasma concentrations of clorazepate, diazepam, estazolam, flurazepam, oral midazolam and triazolam. Thereby, increasing the risk of extreme sedation and respiratory depression from these agents. (For caution on parenterally administered midazolam, see section 4.5.)
Antipsychotic	blonanserin	May result in potential increase in frequency or intensity of known neurological or other toxicities associated with blonaserin.

החמרה אשר התווספה מעלון החברה

Ritonavir is not a cure for HIV-1 infection or AIDS. Patients receiving Ritonavir or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection. While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines. ***Ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer*** *Patients with chronic diarrhoea or malabsorption*: Extra monitoring is recommended when diarrhoea occurs. The relatively high frequency of diarrhoea during treatment with ritonavir may compromise the absorption and efficacy (due to decreased compliance) of ritonavir or other concurrent medicinal products. Serious persistent vomiting and/or diarrhoea associated with ritonavir use might also compromise renal function. It is advisable to monitor renal function in patients with renal function impairment. Renal disease: Since the renal clearance of ritonavir is negligible, the decrease in the total body clearance is not expected in patients with renal impairment. For specific dosing information in patients with renal impairment, refer to the prescribing information of the co-administered protease inhibitor. See also section 4.2. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate in clinical practice (see section 4.8). 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 in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. ***Interactions with other medicinal products:*** ***Ritonavir dosed as an antiretroviral agent*** **Glucocorticoids**: Concomitant use of ritonavir and fluticasone or other glucocorticoids that are metabolised by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression (see section 4.5). **Rivaroxaban**: It is not recommended to use ritonavir in patients receiving rivaroxaban, due to the risk of increased bleeding (see section 4.5).	החמרות אלה התווספו עקב אימוץ העלון האירופאי כלשונו.	***Special warnings and precautions for use***

Interaction with other medicinal products and other forms of interaction

החמרות אלה התווספו עקב אימוץ העלון האירופאי כלשונו.

<u>Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent</u>

Medicinal products that are affected by the use of ritonavir

Interactions between ritonavir and protease inhibitors, antiretroviral agents other than protease inhibitors and other non-antiretroviral medicinal products are listed in the tables below.

Medicinal Product Interactions – Ritonavir with Protease Inhibitors

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of NORVIR (mg)	Medicinal ProductAssessed	AUC	C_{min}
Amprenavir	600 q12h	100 q12h	Amprenavir [2]	↑ 64%	↑ 5 fold
	Ritonavir increases the serum levels of amprenavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 600 mg amprenavir twice daily with ritonavir 100 mg twice daily. Norvir oral solution should not be co-administered with amprenavir oral solution to children due to the risk of toxicity from excipients in the two formulations. For further information, physicians should refer to amprenavir prescribing information.				
Nelfinavir	1250 q12h	100 q12h	Nelfinavir	↑ 20to39 %	ND
	750, single	500 q12h	Nelfinavir	↑ 152%	ND
			Ritonavir	↔	↔
	Ritonavir increases the serum levels of nelfinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination, with respect to efficacy and safety, have not been established. Minimal benefit of ritonavir-mediated pharmacokinetic enhancement is achieved with doses higher than 100 mg twice daily.				

ND: Not determined.
1. Based on cross-study comparison to 400 mg atazanavir once daily alone.
2. Based on cross-study comparison to 1200 mg amprenavir twice daily alone.
3. Based on cross-study comparison to 800 mg indinavir three times daily alone.
4. Based on cross-stud y comparison to 600 mg saquinavir three times daily alone.

Medicinal Product Interactions – Ritonavir with Antiretroviral Agents Other Than Protease Inhibitors

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of NORVIR (mg)	Medicinal Product Assessed	AUC	C_{min}
Didanosine	200 q12h	600 q12h 2 h later	Didanosine	↓ 13%	↔
	As ritonavir is recommended to be taken with food and didanosine should be taken on an empty stomach, dosing should be separated by 2.5 h. Dose alterations should not be necessary.				
Efavirenz	600 q24h	500 q12h	Efavirenz	↑ 21%	
			Ritonavir	↑ 17%	
	A higher frequency of adverse reactions (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.				
Nevirapine	200 q12h	600 q12h	Nevirapine	↔	↔
			Ritonavir	↔	↔
	Co-administration of ritonavir with nevirapine does not lead to clinically relevant changes in the pharmacokinetics of either nevirapine or ritonavir.				
Raltegravir	400 single	100 q12h	Raltegravir	↓ 16%	↓ 1%
	Co-adminsitration of ritonavir and raltegravir results in a minor reduction in raltegravir levels				
Zidovudine	200 q8h	300 q6h	Zidovudine	↓ 25%	ND
	Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose alterations should not be necessary.				

ND: Not determined
1. Based on parallel group comparison.

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Products

Co-administered Medicinal Products	Dose of Co-administered Medicinal Products (mg)	Dose of NORVIR (mg)	Effect on Co-administered Medicinal Products AUC	Effect on Co-administered Medicinal Products C_{max}
Alpha$_1$-Adrenoreceptor Antagonist				

Alfuzosin	Ritonavir co-administration is likely to result in increased plasma concentrations of alfuzosin and is therefore **contraindicated** (see section 4.3).			
Amphetamine Derivatives				
Amphetamine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of amphetamine and its derivatives. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Analgesics				
Buprenorphine	16 q24h	100 q12h	↑ 57%	↑ 77%
Norbuprenorphine			↑ 33%	↑ 108%
Glucuronide metabolites			↔	↔
	The increases of plasma levels of buprenorphine and its active metabolite did not lead to clinically significant pharmacodynamic changes in a population of opioid tolerant patients. Adjustment to the dose of buprenorphine or ritonavir may therefore not be necessary when the two are dosed together. When ritonavir is used in combination with another protease inhibitor and buprenorphine, the SPC of the co-administered protease inhibitor should be reviewed for specific dosing information.			
Pethidine, piroxicam, propoxyphene	Ritonavir co-administration is likely to result in increased plasma concentrations of pethidine, piroxicam, and propoxyphene and is therefore **contraindicated** (see section 4.3).			
Morphine	Morphine levels may be decreased due to induction of glucuronidation by co-administered ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer.			
Antiarrthymics				
Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Ritonavir co-administration is likely to result in increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, and quinidine and is therefore **contraindicated** (see section 4.3).			
Digoxin	0.5 single IV dose	300 q12h, 3 days	↑ 86%	ND

	0.4 single oral dose	200 q12h, 13 days	↑ 22%	↔
	This interaction may be due to modification of P-glycoprotein mediated digoxin efflux by ritonavir dosed as an antriretroviral agent or as a pharmacokinetic enhancer. Increased digoxin levels observed in patients receiving ritonavir may lessen over time as induction develops (see section 4.4)			
Anticoagulant				
Rivaroxaban	10, single dose	600 q12h	↑ 153%	↑ 55%
	Inhibition of CYP3A and P-gp lead to increased plasma levels and pharmacodynamic effects of rivaroxaban which may lead to an increased bleeding risk. Therefore, the use of ritonavir is not recommended in patients receiving rivaroxaban.			
Antidepressants				
Amitriptyline, fluoxetine, imipramine, nortriptyline, paroxetine, sertraline, nefazodone	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of desipramine, imipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine, nefazodone or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.4).			
Antihistamines				
Astemizole, terfenadine	Ritonavir co-administration is likely to result in increased plasma concentrations of astemizole and terfenadine and is therefore **contraindicated** (see section 4.3).			
Fexofenadine	Ritonavir may modify P-glycoprotein mediated fexofenadine efflux when dosed as an antriretroviral agent or as a pharmacokinetic enhancer resulting in increased concentrations of fexofenadine. Increased fexofenadine levels may lessen over time as induction develops.			
Loratadine	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma concentrations of loratadine. Careful monitoring of therapeutic and adverse effects is recommended when loratidine is concomitantly			

	administered with ritonavir.			
Anti-infectives				
Fusidic Acid	Ritonavir co-administration is likely to result in increased plasma concentrations of both fusidic acid and ritonavir and is therefore **contraindicated** (see section 4.3)**.**			
Erythromycin, itraconazole	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of erythromycin and itraconazole. Careful monitoring of therapeutic and adverse effects is recommended when erythromycin or itraconazole is used concomitantly administered with ritonavir.			
Sulfamethoxazole/Trimethoprim[2]	800/160, single dose	500 q12h	↓ 20% / ↑ 20%	↔
	Dose alteration of sulfamethoxazole/trimethoprim during concomitant ritonavir therapy should not be necessary.			
Antipsychotics/Neuroleptics				
Clozapine, pimozide	Ritonavir co-administration is likely to result in increased plasma concentrations of clozapine or pimozide and is therefore **contraindicated** (see section 4.3).			
Haloperidol, risperidone, thioridazine, perphenazine,	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of haloperidol, risperidone, perphenazine and thioridazine. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with antiretroviral doses of ritonavir (see section 4.3).			
Quetiapine	Due to CYP3A inhibition by ritonavir, concentrations of quetiapine are expected to increase. Concomitant administration of Norvir and quetiapine is contraindicated as it may increase quetiapine-related toxicity.			
Calcium channel antagonists				
Amlodipine, diltiazem, nifedipine, verapamil	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of calcium channel antagonists. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.			

Ergot Derivatives			
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore **contraindicated** (see section 4.3).		
GI motility agent			
Cisapride	Ritonavir co-administration is likely to result in increased plasma concentrations of cisapride and is therefore **contraindicated** (see section 4.3).		
HMG Co-A Reductase Inhibitors			
Atorvastatin, Fluvastatin, Lovastatin, Pravstatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A metabolism, such as lovastatin and simvastatin, are expected to have markedly increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Since increased concentrations of lovastatin and simvastatin may predispose patients to myopathies, including rhabdomyolysis, the combination of these medicinal products with ritonavir is **contraindicated** (see section 4.3). Atorvastatin is less dependent on CYP3A for metabolism. While rosuvastatin elimination is not dependent on CYP3A, an elevation of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is not clear, but may be the result of transporter inhibition. When used with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent, the lowest possible doses of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not dependent on CYP3A, and interactions are not expected with ritonavir. If treatment with an HMG-CoA reductase inhibitor is indicated, pravastatin or fluvastatin is recommended.		
Immunosupressants			
Cyclosporine, tacrolimus, everolimus, sirolimus (rapamycin)	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A4 and as a result is expected to increase the plasma concentrations of cyclosporine, tacrolimus, Sirolimus or everolimus. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are concomitantly administered with ritonavir.		

Phosphodiesterase (PDE5) inhibitors				
Avanafil	50, single dose	600 q12h	↑ 13-fold	↑ 2.4-fold
	Concomitant use of avanafil with ritonavir is contraindicated (see section 4.3).			
Sedatives/hynoptics				
Clorazepate, diazepam, estazolam, flurazepam, oral and parenteral midazolam and triazolam	Ritonavir co-administration is likely to result in increased plasma concentrations of clorazepate, diazepam, estazolam and flurazepam and is therefore **contraindicated** (see section 4.3). Midazolam is extensively metabolised by CYP3A4. Co-administration with Norvir may cause a large increase in the concentration of this benzodiazepine. No medicinal product interaction study has been performed for the co-administration of Norvir with benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Therefore, Norvir should not be co-administered with orally administered midazolam (see section 4.3), whereas caution should be used with co-administration of Norvir and parenteral midazolam. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3 – 4 fold increase in midazolam plasma levels. If Norvir is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.			
Triazolam	0.125, single dose	200, 4 doses	↑ > 20 fold	↑ 87%
	Ritonavir co-administration is likely to result in increased plasma concentrations of triazolam and is therefore **contraindicated** (see section 4.3).			
Pethidine Norpethidine metabolite	50, oral single dose	500 q12h	↓ 62% ↑ 47%	↓ 59% ↑ 87%
	The use of pethidine and ritonavir is			

	contraindicated due to the increased concentrations of the metabolite, norpethidine, which has both analgesic and CNS stimulant activity. Elevated norpethidine concentrations may increase the risk of CNS effects (e.g., seizures), see section 4.3.			
Alprazolam	1, single dose	200 q12h, 2 days	↑2.5 fold	↔
		500 q12h, 10 days	↓ 12%	↓ 16%
	Alprazolam metabolism was inhibited following the introduction of ritonavir. After ritonavir use for 10 days, no inhibitory effect of ritonavir was observed. Caution is warranted during the first several days when alprazolam is co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer, before induction of alprazolam metabolism develops.			
Steroids				
Fluticasone propionate aqueous nasal spray	200 µg qd	100 q12h	↑ ~350-fold	↑ ~ 25-fold
	Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression (plasma cortisol levels were noted to be decreased 86% in the above study) have been reported in patients receiving ritonavir and inhaled or intranasal fluticasone propionate; similar effects could also occur with other corticosteroids metabolised by CYP3A e.g., budesonide. Consequently, concomitant administration of ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer and these glucocorticoids is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects (see section 4.4). A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects or a switch to a glucocorticoid, which is not a substrate for CYP3A4 (e.g, beclomethasone). Moreover, in case of withdrawal of glucocorticoids progressive dose reduction may be required over a longer period.			
Dexamethasone	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent inhibits CYP3A and as a result is expected to increase the plasma			

	concentrations of dexamethasone. Careful monitoring of therapeutic and adverse effects is recommended when dexamethasone is concomitantly administered with ritonavir.			
Prednisolone	20	200 q12h	↑ 28%	↑ 9%
	Careful monitoring of therapeutic and adverse effects is recommended when prednisolone is concomitantly administered with ritonavir. The AUC of the metabolite prednisolone increased by 37 and 28% after 4 and 14 days ritonavir, respectively.			
	ND: Not determined 1. Based on a parallel group comparison 2. Sulfamethoxazole was co-administered with trimethoprim.			

Ritonavir dosed as a pharmacokinetic enhancer

Proton pump inhibitors and H_2-receptor antagonists: proton pump inhibitors and H_2-receptor antagonists (e.g. omeprazole or ranitidine) may reduce concentrations for co-administered protease inhibitors. For specific information regarding the impact of co-administration of acid reducing agents, refer to the SmPC of the co-administered protease inhibitor. Based on interaction studies with the ritonavir boosted protease inhibitors (lopinavir/ritonavir, atazanavir), concurrent administration of omeprazole or ranitidine does not significantly modify ritonavir efficacy as a pharmacokinetic enhancer despite a slight change of exposure (about 6 - 18%).

Ritonavir dosed as an antiretroviral agent

Adverse reactions from clinical trials and post-marketing experience in adult patients

The most frequently reported adverse drug reactions among patients receiving ritonavir alone or in combination with other antiretroviral drugs were gastrointestinal (including diarrhea, nausea, vomiting, abdominal pain (upper and lower)), neurological disturbances (including paresthesia and oral paresthesia), rash and fatigue/asthenia.

The following adverse reactions of moderate to severe intensity with possible or probable relationship to Ritonavir have been reported. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness: very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1000 to < 1/100); rare (> 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Events noted as having frequency not known were identified via post-marketing surveillance.

Adverse reactions in clinical studies and post-marketing in adult patients		
System Order Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Common	increased eosinophils
	Uncommon	Increased neutrophils
Immune system disorders	Rare	Anaphylaxis
Metabolic and nutritional disorders	Uncommon	Diabetes mellitus
	Rare	Hyperglycaemia
Nervous system disorders	Very common	headache
	Common	Insomnia, anxiety,
Cardiac disorders	Uncommon	Myocardial infarction
Respiratory, thoracic and mediastinal disorders	Very Common	Pharyngitis,
Gastrointestinal disorders	Common	Anorexia, mouth ulcer, pancreatitis
Skin and subcutaneous tissue disorders	Rare	Stevens Johnson syndrome, Toxic epidermal necrolysis (TEN)

Undesirable effects

Musculosketal and connective tissue disorders	Common	Myositis, rhabdomyolysis		
Renal and urinary disorders	Common	renal impairment (e.g. oliguria, elevated creatinine)		
	Uncommon	Acute renal failure		
Reproductive system and breast disorders	Common	Menorrhagia		
General disorders and administration site conditions	Common	Fever, weight loss		
Investigations	Common	decreased free and total thyroxin		
	Uncommon	Increased glucose, increased magnesium, increased alkaline phosphatase		

Hepatic transaminase elevations exceeding five times the upper limit or normal, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir alone or in combination with other antiretrovirals. Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump). Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4). 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 can occur many months after initiation of treatment (see section 4.4). Pancreatitis has been observed in patients receiving ritonavir therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed. Patients with advanced HIV disease may be at risk of elevated triglycerides and pancreatitis (see section 4.4). 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 (CART). The frequency of this is unknown (see section 4.4).		

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