ANZAVIR-R

Atazanavir (as sulfate) / Ritonavir Tablets
300 mg / 100 mg

Label Code
Each film-coated tablet contains:
Atazanavir (as sulfate) equivalent to Atazanavir 300 mg
Ritonavir USP 100 mg

List of Excipients: Lactose monohydrate (158.00 mg of lactose per tablet), Crospovidone, Microcrystalline cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, Sodium Starch Glycolate, Sorbitan Monolaurate, Colloidal silicon dioxide, Crospovidone, Sunfollow Monohydrate, Film coat (Opadry Orange, Hydroxypropyl methylcellulose, Titanium dioxide, PEG, Polydextrose and Iron oxide red)

Therapeutic Indications
The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets are indicated in HIV-1 infected adults in combination with other antiretroviral medicinal products.
Based on available virological and clinical data from treatment-naive patients, no benefit is expected in patients with viruses resistant to multiple protease inhibitors (i.e. ≥ 3 PI resistance).
The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets is treatment experienced adult and paediatric patients should be treated on evidence and resistance testing and their treatment history.

Posology and method of administration
Therapy should be initiated by a physician experienced in the management of HIV infection.
Adults: The recommended dose of the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets is once daily taken with food. The dose of the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets should be swallowed whole and not chewed, broken or crushed.
Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years.
Special populations

Patients with renal impairment: No dosage adjustment is needed. The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets should be used with caution in these patients.
Patients with hepatic impairment: The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets should be used in patients with hepatic impairment. The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets should be used with caution in patients with mild hepatic impairment (Child-Pugh Class A). The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets should not be used in patients with moderate to severe hepatic impairment.

Pregnancy and Postpartum
during the second and third trimesters of pregnancy
The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets may not provide sufficient exposure to atazanavir, especially in the third trimester of pregnancy. Therefore, the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets is not available and that to inter-patient variability during pregnancy. Therapeutic Drug Monitoring (TDM) may be considered to ensure adequate exposure.
The use of a further decrease in atazanavir exposure is expected when atazanavir is given with medicinal products known to induce its exposure (e.g. tenofovir, any ritonavir antagonists).
- If tenofovir or any ritonavir antagonist is needed, a dose increase to Atazanavir (as sulfate) 400 mg with ritonavir 100 mg with TDM is recommended.
- It is not recommended to use the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets in pregnant patients who are receiving both tenofovir and an H2-receptor antagonist.

During postpartum period
Following 2 weeks after the initiation of atazanavir exposure during the second and third trimester, atazanavir exposures might increase during the first two months after delivery. Therefore, postpartum patients should be closely monitored for adverse reactions.

- The dose of the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets can be maintained patients, including those receiving tenofovir or any H2-receptor antagonist.
- No co-administration of medicinal products known to affect atazanavir exposure.

Contraindications
The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets are contraindicated in patients with known hypersensitivity to atazanavir, ritonavir, or any of the excipients.

Warnings
Patients with moderate to severe hepatic insufficiency.
Co-administration of the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets with simvastatin or lovastatin is contraindicated.
Combination of Atazanavir (as sulfate) and ritonavir with salmeterol (as sulfate)/Ritonavir 300mg/100mg tablets is contraindicated as dose increase of salmeterol may be associated with cardiac events.
Co-administration is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) only for co-administration with sildenafil for the treatment of erectile dysfunction due to lack of safety and prescription for use of Atazanavir (as sulfate) medicinal products and other forms of interaction.
Co-administration is contraindicated when used in combination with medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and for which plasma therapeutic variations (e.g. alfuzosin, astemizole, cisapride, quinidine, bepridil, triazolam, midazolam administered orally (for caution in parenterally administered midazolam see - Interaction with other medicinal products and other forms of interaction) may be associated with serious and/or life-threatening events.
Atazanavir (as sulfate) must not be used in combination with products containing St. John's wort (Hypericum perforatum).

Ritonavir
Ritonavir should not be given as a pharmacokinetic enhancer at an undersized dose to avoid the development of viral resistance.
In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformation. The significance of this inhibitory property of ritonavir (with or without other protease inhibitors) on the safety and efficacy of concomitantly administered medicinal products is discussed in the following sections. Ritonavir is also a moderate inhibitor of CYP2C19. Ritonavir is also an inducer of CYP1A2, CYP2C9, CYP3A, and UGTs. Induction may increase the biotransformation of certain medicinal products. Clinically significant interactions are discussed in the following sections.
Important information regarding drug interactions when ritonavir is used as a pharmacokinetic enhancer is also contained in the Summary of Product Characteristics of the co-administered protease inhibitor.

Medicinal Product Class	Medicinal Product within Class	Rationale
Concomitant Drug Levels Increased or Decreased		
α_1-Adrenoceptor Antagonist	Alfuzosin	Increased plasma concentrations of alfuzosin which may lead to severe hypotension.
Analgesics	Pethidine, piroxicam, propoxyphene	Increased plasma concentrations of norpethidine which may lead to convulsions. Thereby, increasing the risk of severe respiratory depression or haemorrhagic diathesis respectively. Ritonavir does not alter plasma concentrations of propoxyphene or piroxicam.
Antiarrhythmics	Amiodarone, bepridil, encainide, flecainide, propafenone, quinidine	Increased plasma concentrations of amiodarone, bepridil, encainide, flecainide, propafenone, quinidine. Thereby, increasing the risk of cardiac arrhythmias or other adverse effects from these agents.
Antibiotic	Fusidic Acid	Increased plasma concentrations of fusidic acid and ritonavir.
Antifungal	Voriconazole	Concomitant use of ritonavir (400 mg twice daily and more) and voriconazole is contraindicated due to a reduction in voriconazole exposure and loss of the possible loss of effect.
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 (boosted as an antiretroviral agent) and rifabutin increases rifabutin AUC by 4-fold, serum concentrations and risk of adverse reactions (e.g. uveitis). Ritonavir also has a significant effect on the metabolism of other antimycobacterial agents (e.g. clarithromycin) which may also result in increased pharmacokinetic enhancer with rifabutin and/or metabolites of rifabutin to accumulate. Dosing recommendations are provided in the Summary of Product Characteristics for these medicinal products.
Antipsychotics/ Neuroleptics	Clozapine, pimozide	Increased plasma concentrations of clozapine and pimozide. Thereby, increasing the risk of serious reactions. Co-administration of clozapine and pimozide is contraindicated.
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Increased plasma concentrations of ergot derivatives which may lead to acute ergot toxicity including vasospasm and ischaemia.
GI motility agent	Cisapride	Increased plasma concentrations of cisapride. Thereby, increasing the risk of arrhythmias from this agent.
HMG-CoA Reductase Inhibitor	Lovastatin, simvastatin	Increased plasma concentrations of lovastatin and simvastatin. Thereby, increasing the risk of myopathy including rhabdomyolysis.
PDE5 inhibitor	Sildenafil	Sildenafil plasma concentrations when used for the treatment of pulmonary arterial hypertension (PAH). Co-administration of sildenafil with ritonavir is contraindicated. Co-administration with other medicinal products and other forms of interaction.
Ritonavir Medicinal product Level Decreased		
Herbal Preparations	St. John's Wort	Herbal preparations containing St. John's wort (Hypericum perforatum) due to the risk of decreased plasma concentrations and reduced clinical effects of ritonavir.

Special warning and precautions for use
The fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets are not a cure for HIV-1 infection or AIDS. Patients receiving the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV-1 infection.
Patients should be advised that current antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through blood or sexual contact. Appropriate precautions should continue to be employed.

Hepatic disease
Safety and efficacy of the fixed dose combination Atazanavir (as sulfate)/Ritonavir 300mg/100mg tablets have not been clinically evaluated. The use of higher ritonavir doses might alter the safety profile of atazanavir (cardiac effects, hepatobiliary) and therefore is not recommended. Patients with underlying hepatitis B or C, or severe elevations of transaminases before treatment are at increased risk of liver function abnormalities. In this instance, close clinical monitoring is warranted. See Interaction with other Medicinal Products below.
Patients with co-existing conditions

Hepatic impairment: Ritonavir is primarily hepatically metabolised and increased plasma concentrations were observed in patients with hepatic impairment. The safety and efficacy of Atazanavir (as sulfate) has not been established in patients with significant underlying liver disorders. Ritonavir should be used with caution in patients with mild hepatic impairment (Child-Pugh Class A) as there is a potential for potentially fatal hepatic reactions. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant Summary of Product Characteristics for these medicinal products.
Haemophilia: Protease inhibitors, including ritonavir, have been reported in patients with haemophilia A and B treated concomitantly during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.
Diabetes: Hyperglycaemia, new onset diabetes mellitus, hyperglycaemia and exacerbation of pre-existing diabetes mellitus have been reported in protease inhibitors. Diabetic patients should be informed of the potential for an increase in blood glucose. Ketoacidosis has occurred in some patients receiving protease inhibitors. In patients with pre-existing risk factors, consideration should be given to second degree or higher atrioventricular conduction abnormalities. Atazanavir (as Sulfate) should be used with caution and only when the benefits outweigh the risks in patients with pre-existing risk factors (bradycardia, long conduction intervals which have the potential to become the AV interval and/or in patients with pre-existing risk factors (bradycardia, long conduction ECG electrolyte imbalances).
Immune reactivation: Patients who have been injects of increased bleeding, including spontaneous skin haematomas and haemarthroses, in type A and B haemophiliac patients treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been postulated between the temporary withdrawal of protease inhibitor therapy and rebleeding. Moreover, a causal relationship between the protease inhibitor mechanism of action has not been established. Haemophiliac patients should therefore be informed of the possibility of increased bleeding.
Autoimmune disorders: Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have been reported to occur after the initiation of immune reconstitution therapy. The reported median time to onset is variable and can be more than one year after initiation of treatment. Patients should be monitored for signs of inflammation from previously asymptomatic or residual opportunistic infections that may necessitate evaluation and treatment.
Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), 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 and other forms of interaction

Atazanavir
Co-administration of Atazanavir (as sulfate) with simvastatin or lovastatin is not recommended.
Co-administration of Atazanavir (as sulfate) with lovastatin or simvastatin is contraindicated.
If the co-administration of Atazanavir (as sulfate) with an MAPI is required, an increase in the dose of both Atazanavir (as sulfate) and ritonavir to 400 mg and 200 mg, respectively, in combination with efavirenz should be considered with close clinical monitoring.
Atazanavir is metabolised principally by CYP3A. Co-administration of Atazanavir (as sulfate) with ritonavir and medicinal products that induce CYP3A may result in decreased exposure to Atazanavir (as sulfate) and ritonavir and may result in loss of therapeutic response and possible development of resistance.
PDE5 inhibitors used for the treatment of erectile dysfunction (sildenafil, tadalafil, vardenafil) should be used when prescribing PDE5 inhibitors together with Atazanavir (as sulfate) and ritonavir. Co-administration of Atazanavir (as sulfate) with these medicinal products is expected to substantially increase their concentrations and may increase the number of adverse reactions associated with these medicinal products.
Co-administration of Atazanavir (as sulfate) with ritonavir is not recommended when used for the treatment of pulmonary arterial hypertension (PAH) due to potentially increased risk of adverse reactions associated with PDE5 inhibitors (e.g. visual disturbances, priapism and hypotension) and limited data on safety.
Co-administration of Atazanavir (as sulfate) with ritonavir and medicinal products that are substrates of the CYP3A4 isoform of cytochrome P450 and for which plasma therapeutic variations (e.g. alfuzosin, astemizole, cisapride, bepridil, triazolam, midazolam administered orally (for caution in parenterally administered midazolam see - Interaction with other medicinal products and other forms of interaction) may be associated with serious and/or life-threatening events.
Atazanavir (as sulfate) must not be used in combination with products containing St. John's wort (Hypericum perforatum).

Ritonavir
Ritonavir should not be given as a pharmacokinetic enhancer at an undersized dose to avoid the development of viral resistance.
In vitro and *in vivo* studies have demonstrated that ritonavir is a potent inhibitor of CYP3A- and CYP2D6- mediated biotransformation. The significance of this inhibitory property of ritonavir (with or without other protease inhibitors) on the safety and efficacy of concomitantly administered medicinal products is discussed in the following sections. Ritonavir is also a moderate inhibitor of CYP2C19. Ritonavir is also an inducer of CYP1A2, CYP2C9, CYP3A, and UGTs. Induction may increase the biotransformation of certain medicinal products. Clinically significant interactions are discussed in the following sections.
Important information regarding drug interactions when ritonavir is used as a pharmacokinetic enhancer is also contained in the Summary of Product Characteristics of the co-administered protease inhibitor.

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of Ritonavir (mg)	Medicinal Product Effect Concentrations	AUC	C_{min}
Atazanavir	400 qd with food	100 qd with food	Atazanavir*	↑ 64%	↑ 157%
Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 300 mg atazanavir once daily with ritonavir 100 mg once daily in treatment experienced patients. Atazanavir should not be co-administered with ampranavir and solution to dilution for the boost of toxicity from exceptions of the CYP3A4 isoform of cytochrome P450. For further information, please see the Summary of Product Characteristics.					
Amprenavir	600 qd with food	100 qd with food	Amprenavir*	↑ 64%	↑ 141%
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 in treatment experienced patients. Amprenavir should not be co-administered with ampranavir and solution to dilution for the boost of toxicity from exceptions of the CYP3A4 isoform of cytochrome P450. For further information, please see the Summary of Product Characteristics.					
Atazanavir	300 qd with food	100 qd with food	Atazanavir*	↑ 66%	↑ 11 fold
			Ritonavir*	↑ 2 fold	↑ 3 fold
Ritonavir increases the serum levels of atazanavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 300 mg atazanavir once daily with ritonavir 100 mg once daily in treatment experienced patients. Atazanavir should not be co-administered with ampranavir and solution to dilution for the boost of toxicity from exceptions of the CYP3A4 isoform of cytochrome P450. For further information, please see the Summary of Product Characteristics for Prostrata.					
Darunavir	600, single dose	100 qd with food	Darunavir	↑ 14 fold	
Ritonavir increases the serum levels of darunavir as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of 600 mg darunavir twice daily with ritonavir 100 mg twice daily in treatment experienced patients with darunavir. For further information, refer to the Summary of Product Characteristics for Prostrata.					
Fosamprenavir	700 qd	100 qd	Amprenavir*	↑ 77%	↑ 2.5 fold
Ritonavir increases the serum levels of amprenavir (fosamprenavir) as a result of CYP3A4 inhibition. Clinical trials confirmed the safety and efficacy of fosamprenavir 700 mg twice daily with ritonavir 100 mg twice daily. Ritonavir doses higher than 100 mg twice daily have not been studied in combination with fosamprenavir. For further information, please see the Summary of Product Characteristics for Prostrata or Fortovase 700 mg twice daily.					
Indinavir	800 q12h	100 q12h	Indinavir*	↑ ~20 fold	↑ ~29 fold
			Ritonavir †	↑ 72%	ND
	400 q12h	400 q12h	Indinavir*	↔	↑ 1 fold
			Ritonavir	↔	↔
Ritonavir increases the serum levels of indinavir as a result of CYP3A4 inhibition. Appropriate doses for this combination have been established in clinical trials. Indinavir should be used with caution in combination with ritonavir in patients with mild to moderate liver disease. Ritonavir also has a high affinity for CYP2D6 and can inhibit the metabolism of other substrates of this isoform. Co-administration of ritonavir (100 mg twice daily) and indinavir (800 mg twice daily) is expected to increase the plasma concentrations of indinavir.					
Nelfinavir	1250 q12h	100 q12h	Nelfinavir	↑ 20 to 39%	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 have been established in clinical trials. Nelfinavir should be used with caution in combination with ritonavir in patients with mild to moderate liver disease. Ritonavir also has a high affinity for CYP2D6 and can inhibit the metabolism of other substrates of this isoform. For further information, please see the Summary of Product Characteristics for Viracept.					
Saquinavir	1000 q12h	100 q12h	Saquinavir*	↑ 13 fold	↑ 5 fold
			Ritonavir	↔	↔
	400 q12h	400 q12h	Saquinavir*	↑ 20 fold	↑ 17 fold
			Ritonavir	↔	↔
Ritonavir increases the serum levels of saquinavir as a result of CYP3A4 inhibition. Saquinavir should only be co-administered with ritonavir as part of a regimen containing low dose ritonavir to ensure therapeutic effect. Doses of ritonavir less than 400 mg twice daily should not be used in combination with saquinavir. Ritonavir also has a high affinity for CYP2D6 and can inhibit the metabolism of other substrates of this isoform. For further information, please see the Summary of Product Characteristics for Invirase.					
Tipranavir	500 q12h	200 q12h	Tipranavir	↑ 11 fold	↑ 29 fold
			Ritonavir	↓ 40%	ND
Ritonavir increases the serum levels of tipranavir as a result of CYP3A4 inhibition. Tipranavir should be given with low dose ritonavir to ensure therapeutic effect. Doses of ritonavir less than 200 mg twice daily should not be used in combination with tipranavir. For further information, please see the Summary of Product Characteristics for Aptivus.					

ND: Not determined
↑: 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 1000 mg saquinavir twice daily alone.
4. Based on cross-study comparison to 500 mg/200 mg tipranavir twice 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 Ritonavir (mg)	Medicinal Product Effect Concentrations	AUC	C_{min}
Didanosine	250 q12h	600 q12h 2h Didanosine	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 h. There should also be separated by 2 h. See also prescribing information for didanosine.					
Dolutegravir	400 qd	600 q12h	Dolutegravir*	↓ 40%	↓ 71%
	600 q12h	600 q12h	Dolutegravir*	↓ 21%	↓ 71%
Based on comparison to historical data. No pharmacokinetic of atazanavir did not appear to be affected by ritonavir. Effect also could on combination abacavir, dose reduction of dolutegravir may be considered.					
Efavirenz	600 q24h	500 q12h	Efavirenz	↑ 21%	
			Ritonavir	↑ 17%	
A higher frequency of adverse events (e.g., dizziness, impaired concentration, abnormal dreams, somnolence) (elevated liver enzymes) have been observed when efavirenz is co-administered with ritonavir dosed as an antiretroviral agent.					
Maraviroc	100 q12h	100 q12h	Maraviroc	↑ 161%	↑ 78%
Ritonavir increases the serum levels of maraviroc as a result of CYP3A4 inhibition. Maraviroc should be used with caution in patients with ritonavir to increase the maraviroc exposure. For further information, refer to the Summary of Product Characteristics for Celsentri.					
Nevirapine	200 q12h	600 q12h	Nevirapine	↔	↔
	200 qd	300 q12h	Nevirapine	↑ 28%	↑ 11%
Co-administration of Ritonavir with nevirapine does not lead to clinically relevant changes in the pharmacokinetics of either agent at ritonavir.					
Zidovudine	200 q8h	300 q8h 2h Zidovudine		↓ 25%	ND
Ritonavir may induce the glucuronidation of zidovudine, resulting in slightly decreased levels of zidovudine. Dose adjustments are not required.					

ND: Not determined
↑: Based on graphical comparison.

Ritonavir effects on Non-antiretroviral Co-administered Medicinal Product

Co-administered Medicinal Product	Dose of Co-administered Medicinal Product (mg)	Dose of Ritonavir (mg)	Effect on Co-administered Medicinal Product AUC	Effect on Co-administered Medicinal Product C_{max}
Alpha1 -Adrenoceptor Antagonist				
Alfuzosin	Should not be co-administered with ritonavir due to increased plasma concentrations of alfuzosin and a therefore potentially severe hypotension.			
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 amphetamine and its derivatives are co-administered with ritonavir dosed as an antiretroviral agent.			
Analgesics				
Buprenorphine	16 q24h	100 q12h	↑ 51%	↑ 71%
Norbuprenorphine			↑ 33%	↑ 108%
Glucuronide metabolites			↔	↔
Tramadol	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 when co-administered with ritonavir dosed as an antiretroviral agent is not expected to be necessary. However, protease inhibitor and ritonavir may induce the metabolism of tramadol and lead to decreased plasma concentrations of tramadol. Ritonavir inhibits should be monitored for opioid dosing alternatives.			
Pethidine, piroxicam, propoxyphene	Should not be co-administered as increased plasma concentrations of norpethidine, piroxicam, propoxyphene and a therefore potentially severe adverse events.			
Fentanyl	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 fentanyl. Careful monitoring of therapeutic and adverse effects is recommended when fentanyl is co-administered with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent.			
Anticoagulants				
Warfarin	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent alters warfarin concentrations. Monitoring of anticoagulant activity is recommended when warfarin is co-administered with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent.			
Anticonvulsants				
Carbamazepine	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 carbamazepine. Careful monitoring of therapeutic and adverse effects is recommended when carbamazepine is co-administered with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent.			
Phenytoin, phenobarbital, valproate	Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent induces oxidation by CYP3A and as a result is expected to increase the clearance of phenytoin, phenobarbital and valproate. Careful monitoring of serum levels is therefore recommended when these medicines are co-administered with ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent.			
Antidepressants				
Amitriptyline, desipramine, fluoxetine, nortriptyline, paroxetine, sertraline, trazodone, venlafaxine	Ritonavir dosed as an antiretroviral agent is likely to inhibit CYP2D6 and as a result is expected to increase concentrations of desipramine, amitriptyline, nortriptyline, fluoxetine, paroxetine or sertraline. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are co-administered with ritonavir dosed as an antiretroviral agent.			
Desipramine	100 mg/8 oral dose	500 q12h	↑ 145%	↑ 22%
	50, single dose	200 q12h	↑ 2.4 fold	↑ 4 fold
Trazodone	An increase in the incidence of adverse events was noted when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. If ritonavir is co-administered with trazodone, a dose reduction of trazodone may be necessary. Careful monitoring for clinical response and tolerability is recommended.			
Anti-gout treatments				
Colchicine	Concentrations of colchicine are expected to increase when coadministered with ritonavir.			
Anthelmintics				
Albendazole, ketoconazole, praziquantel	Ritonavir co-administration is likely to result in increased plasma concentrations of albendazole and praziquantel. Ritonavir may modify Pyrazoquinolin-mediated fasciolicide effect when dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Ritonavir co-administration is likely to increase the plasma concentrations of ketoconazole.			
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.			
Rifabutin*	150 daily	300 q12h, 7 d	↑ 4 fold	↑ 2.3 fold
25-O-desacetyl rifabutin metabolite			↑ 31 fold	↑ 16 fold
Due to the large increase in rifabutin AUC, the concomitant use of rifabutin with ritonavir dosed as an antiretroviral agent is not recommended. Rifabutin is a substrate of CYP3A4 and ritonavir is a strong inhibitor of CYP3A4. Rifabutin exposure is increased by 4-fold when co-administered with ritonavir dosed as an antiretroviral agent. Refer to the Summary of Product Characteristics of the co-administered protease inhibitor should be consulted for recommendations regarding dose adjustments of rifabutin. Additional monitoring for rifabutin adverse reactions including uveitis is recommended.				
Although rifampicin may induce metabolism of ritonavir, limited data indicate that when high doses of ritonavir (600 mg twice daily) are co-administered with rifampicin (600 mg once daily), the AUC of ritonavir is reduced to that of ritonavir dosed alone. Ritonavir should be used with caution when co-administered with rifampicin.				
Rifampicin	600 q24h	300 q12h	↓ 35%	↓ 25%
	600 q24h	400 q12h	↓ 42%	↓ 66%
	600 q24h	500 q12h	↓ 72%	↓ 76%
Voriconazole	Concomitant use of ritonavir dosed as an antiretroviral agent and voriconazole is contraindicated due to a reduction in voriconazole exposure and loss of the possible loss of effect. Ritonavir is also a potent inhibitor of CYP3A4 and has the potential to increase voriconazole exposure when co-administered with ritonavir dosed as an antiretroviral agent. Careful monitoring of therapeutic and adverse effects is recommended when voriconazole is co-administered with ritonavir.			
Atovaquone	Ritonavir co-administration is likely to result in increased plasma concentrations of atovaquone and as a result is expected to decrease the plasma concentrations of atovaquone. Careful monitoring of therapeutic and adverse effects is recommended when these medicines are co-administered with ritonavir.			
Endothelin antagonists				
Bosentan	Co-administration of bosentan and ritonavir may increase steady state bosentan maximum concentr atoms and is therefore contraindicated.			
Ergot Derivatives				
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Ritonavir co-administration is likely to result in increased plasma concentrations of ergot derivatives and is therefore contraindicated.			
GI motility agent				
Cisapride	Ritonavir co-administration is likely to result in increased plasma concentrations of cisapride and is therefore contraindicated.			
HMG CoA Reductase Inhibitors				
Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin	HMG-CoA reductase inhibitors which are highly dependent on CYP3A4 metabolism, such as lovastatin and simvastatin, are expected to have increased plasma concentrations when co-administered with ritonavir dosed as an antiretroviral agent or as a pharmacokinetic enhancer. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy including rhabdomyolysis. Based on data for other CYP3A4 inhibitors, pharmacokinetic interactions of atorvastatin are expected to be less marked than those observed with lovastatin and simvastatin. Atorvastatin is also a substrate for CYP3A4, as ritonavir, of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is unknown. Co-administration of ritonavir with HMG-CoA reductase inhibitors should be undertaken with caution and the lowest dose of atorvastatin or rosuvastatin should be administered. The metabolism of pravastatin and fluvastatin is not significantly affected by CYP3A4 inhibition. Therefore, ritonavir is not expected to affect the plasma concentrations of these medicinal products. Ritonavir is also a substrate for CYP2C9, as inhibition of rosuvastatin exposure has been reported with ritonavir co-administration. The mechanism of this interaction is unknown. Co-administration of ritonavir with HMG-CoA reductase inhibitors should be undertaken with caution and the lowest dose of

ANZAVIR-R

Atazanavir (sous forme de sulfate) / Ritonavir Comprimés
300 mg / 100 mg

Composition qualitative et quantitative
Atazanavir 300 mg (sous forme de sulfate)
Ritonavir (sous forme de sulfate) équivalent à Ritonavir 100 mg
Excipient: Lactose.
Excipients: Carbonate: Lactose monohydraté (148,80 mg de lactose par comprimé), Croscarmellose, Cellulose microcristalline, Silicate de magnésium, Glycérol de sodium, Fumarate de stéaryl sodique, Soluté, Arabite de mais, Dioxyde de silicium colloïdale, Copolymère, Monohydrate de sorbitan, polysorbate (Hypromellose, Polyethylène glycol 400, Polyethylène glycol 8000).

Indications thérapeutiques
Traitement de l'infection à VIH: Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés crée les patients antirétroviraux, dans le traitement de l'infection par le VIH-1 chez l'adulte.
Adultes: La dose recommandée de l'association d'Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés doit être suivie par voie de la manière suivante: L'association à dose fixe Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés doit être suivie par voie de la manière suivante: 1 comprimé par jour pris avec la nourriture.
Personnes âgées: Il n'y a pas de données disponibles permettant d'établir une recommandation posologique pour les patients âgés de 65 ans et plus.

Populations particulières
Patients présentant une insuffisance rénale: Aucune adaptation posologique n'est nécessaire. L'association à dose fixe Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés ne doit pas être administrée chez les patients présentant une insuffisance rénale sévère (clairance de la créatinine inférieure à 30 ml/min).
Patients présentant une insuffisance hépatique: L'association à dose fixe Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés ne doit pas être administrée chez les patients présentant une insuffisance hépatique modérée à sévère.

Mode d'administration
Voie orale
Prendre le second comprimé d'Atazanavir, et la grossesse.
L'association à dose fixe Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés pourrait ou pas permettre d'atteindre une concentration plasmatique d'Atazanavir suffisante pour obtenir une réponse virologique optimale. Si un comprimé de 150 mg d'Atazanavir est nécessaire, il est recommandé de prendre l'association à dose fixe Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés avec la nourriture.
Les comprimés ne doivent pas être mâchés, écrasés ou coupés. Ils doivent être avalés entiers avec de l'eau.

Contre-indications
L'association à dose fixe Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés sont contre-indiquées chez les patients présentant l'une des situations suivantes:
- Hypersensibilité à la substance active ou à l'un des excipients.
- Patients présentant une insuffisance hépatique modérée à sévère.
- Patients recevant simultanément l'un des médicaments suivants: Alcaloïdes dérivés de l'ergot de seigle, par exemple dihydroergotamine, ergométrine, ergotamine, méthylergométrine (voir rubrique «Interactions»).
- Patients recevant simultanément l'un des médicaments suivants: Astémizole, terfénadine, amiodarone, quinidine, bépridil, bosentan, lovastatine, simvastatine, midazolam administré par voie orale, triazolam, pimozide, sildénafil utilisé pour le traitement de l'hypertension artérielle pulmonaire, halofantrine, dérivés de l'ergot de seigle, par exemple ergotamine, dihydroergotamine, méthylergométrine, ergométrine (voir rubrique «Interactions»).
- Patients présentant une hypersensibilité à l'arachide ou au soja (Ritonavir comprimés).

Mises en garde spéciales et précautions d'emploi
L'association à dose fixe Atazanavir (sous forme de sulfate)/Ritonavir 300mg/100mg comprimés ne guérit pas de l'infection par le VIH-1 ou le SIDA. Les patients doivent être informés que les traitements antirétroviraux actuellement disponibles, y compris Atazanavir, ne peuvent pas empêcher la transmission du VIH par contact sexuel ou par contamination sanguine. Les patients doivent être informés que les traitements antirétroviraux actuellement disponibles, y compris Atazanavir, ne peuvent pas diminuer le risque de transmission du VIH. Par conséquent, des précautions appropriées doivent être maintenues.

Ictères
La co-administration d'Atazanavir (sous forme de sulfate) avec du Ritonavir a été associée à des ictères dus à l'hyperbilirubinémie non conjuguée. Ceci est dû à l'inhibition de l'UGT1A1 par Atazanavir et Ritonavir. Les ictères ont été observés chez des patients recevant Atazanavir sans Ritonavir et peuvent être plus fréquents lorsque l'association d'Atazanavir et Ritonavir est co-administrée. Les patients qui présentent une hyperbilirubinémie non conjuguée due à Atazanavir ne sont pas forcément à risque accru d'hépatotoxicité. Les patients qui présentent une hépatotoxicité et qui ont besoin d'un traitement antirétroviral peuvent envisager de substituer Atazanavir par un autre médicament antirétroviral.

Patients avec pathologies sanguines
Insuffisance hépatique: L'atazanavir est principalement métabolisé par le foie et des concentrations plasmatiques élevées ont été observées chez les patients présentant une insuffisance hépatique. Les patients souffrant d'une insuffisance hépatique légère ou modérée (Child-Pugh classe A ou B) n'exigent pas une adaptation de la dose d'Atazanavir, mais ces patients doivent être surveillés étroitement. Atazanavir n'a pas été étudié chez les patients présentant une insuffisance hépatique sévère (Child-Pugh classe C) et ne doit pas être administré à ces patients.
Augmentation de l'intervalle QT: Des augmentations asymptomatiques de l'espace PR liés à la dose ont été observées chez des patients recevant Atazanavir. Des cas de bloc auriculo-ventriculaire du premier degré ont été rapportés. Des augmentations de l'espace PR doivent être utilisés avec précaution. Chez les patients ayant des antécédents de troubles de la conduction cardiaque chez des patients recevant Atazanavir