

Indinavir capsules

INDIVAN

COMPOSITION

INDIVAN -200 Capsules

Each capsule contains Indinavir sulphate equivalent to Indinavir 200 mg

INDIVAN - 400 Capsules

Each capsule contains Indinavir Sulphate equivalent to Indinavir 400 mg

DOSAGE FORM

Oral capsules

PHARMACOLOGY

Pharmacodynamics

HIV-1 protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV-1. Indinavir binds to the protease active site and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature non-infectious viral particles.

Pharmacokinetics

Absorption: Indinavir was rapidly absorbed in the fasted state with a time to peak plasma concentration (T_{max}) of 0.8 ± 0.3 hours (mean \pm S.D.) (n=11). A greater than dose-proportional increase in indinavir plasma concentrations was observed over the 200-1000 mg dose range. At a dosing regimen of 800 mg every 8 hours, steady-state area under the plasma concentration time curve (AUC) was $30,691 \pm 11,407$ nM•hour (n=16), peak plasma concentration (C_{max}) was $12,617 \pm 4037$ nM (n=16), and plasma concentration eight hours post dose (trough) was 251 ± 178 nM (n=16).

Effect of Food on Oral Absorption

Administration of indinavir with a meal high in calories, fat, and protein (784 kcal, 48.6 g fat, 31.3 g protein) resulted in a $77\% \pm 8\%$ reduction in AUC and an $84\% \pm 7\%$ reduction in C_{max} (n=10). Administration with lighter meals (e.g., a meal of dry toast with jelly, apple juice, and coffee with skim milk and sugar or a meal of corn flakes, skim milk and sugar) resulted in little or no change in AUC, C_{max} or trough concentration.

Distribution: Indinavir was approximately 60% bound to human plasma proteins over a concentration range of 81 nM to 16,300 nM.

Metabolism: Following a 400-mg dose of ¹⁴C-indinavir, 83 ± 1% (n=4) and 19 ± 3% (n=6) of the total radioactivity was recovered in feces and urine, respectively; radioactivity due to parent drug in feces and urine was 19.1% and 9.4%, respectively. Seven metabolites have been identified, one glucuronide conjugate and six oxidative metabolites. *In vitro* studies indicate that cytochrome P-450 3A4 (CYP3A4) is the major enzyme responsible for formation of the oxidative metabolites.

Elimination: Less than 20% of indinavir is excreted unchanged in the urine. Mean urinary excretion of unchanged drug was 10.4 ± 4.9% (n=10) and 12.0 ± 4.9% (n=10) following a single 700-mg and 1000-mg dose, respectively. Indinavir was rapidly eliminated with a half-life of 1.8 ± 0.4 hours (n=10). Significant accumulation was not observed after multiple dosing at 800 mg every 8 hours.

Special Populations

Hepatic Insufficiency: Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of indinavir resulting in approximately 60% higher mean AUC following a single 400-mg dose (n=12). The half-life of indinavir increased to 2.8 ± 0.5 hours. Indinavir pharmacokinetics have not been studied in patients with severe hepatic insufficiency (see **DOSAGE AND ADMINISTRATION**, Hepatic Insufficiency).

Renal Insufficiency: The pharmacokinetics of indinavir have not been studied in patients with renal insufficiency.

Gender: The effect of gender on the pharmacokinetics of indinavir was evaluated in 10 HIV seropositive women who received indinavir 800 mg every 8 hours with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day for one week. Indinavir pharmacokinetic parameters in these women were compared to those in HIV seropositive men (pooled historical control data).

Differences in indinavir exposure, peak concentrations, and trough concentrations between males and females are shown in Table 1 below:

Table 1

| PK Parameter | % change in PK parameter for females relative to males | 90% Confidence Interval |
|-----------------------------|--|-------------------------|
| AUC _{0-8h} (nM•hr) | ↓13% | (↓32%, ↑12%) |
| C _{max} (nM) | ↓13% | (↓32%, ↑10%) |
| C _{8h} (nM) | ↓22% | (↓47%, ↑15%) |

↓ Indicates a decrease in the PK parameter; ↑ Indicates an increase in the PK parameter.

The clinical significance of these gender differences in the pharmacokinetics of indinavir is not known.

Pediatric: The optimal dosing regimen for use of indinavir in pediatric patients has not been established. In HIV-infected pediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m² every 8 hours, produced AUC_{0-8hr} of 38,742 ± 24,098 nM•hour (n=34), C_{max} of 17,181 ± 9809 nM (n=34), and trough concentrations of 134 ± 91 nM (n=28).

The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to profiles previously observed in HIV-infected adults receiving the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and the trough concentrations were considerably lower in pediatric patients. Approximately 50% of the pediatric patients had trough values below 100 nM; whereas, approximately 10% of adult patients had trough levels below 100 nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

Pregnant Patients: The optimal dosing regimen for use of indinavir in pregnant patients has not been established. A indinavir dose of 800 mg every 8 hours (with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day) has been studied in 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). The mean indinavir plasma AUC_{0-8hr} at weeks 30-32 of gestation (n=11) was 9231 nM•hr, which is 74% (95% CI: 50%, 86%) lower than that observed 6 weeks postpartum. Six of these 11 (55%) patients had mean indinavir plasma concentrations 8 hours post-dose (C_{min}) below assay threshold of reliable quantification. The pharmacokinetics of indinavir in these 11 patients at 6 weeks postpartum were generally similar to those observed in nonpregnant patients in another study (see **WARNINGS AND PRECAUTIONS**, Pregnancy).

INDICATIONS

INDIVAN in combination with antiretroviral agents is indicated for the treatment of HIV infection.

DOSAGE AND ADMINISTRATION

The recommended dosage of indinavir is 800 mg (usually two 400-mg capsules) orally every 8 hours. Indinavir must be taken at intervals of 8 hours. For optimal absorption, indinavir should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, indinavir may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, e.g., dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar (see **PHARMACOKINETICS**; *Effect of Food on Oral absorption*). To ensure adequate hydration, it is recommended that adults drink at least 1.5 liters (approximately 48 ounces) of liquids during the course of 24 hours.

Concomitant therapy

Delavirdine

Dose reduction of indinavir to 600 mg every 8 hours should be considered when administering delavirdine 400 mg three times a day.

Didanosine

If indinavir and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach.

Itraconazole

Dose reduction of indinavir to 600 mg every 8 hours is recommended when administering itraconazole 200 mg twice daily concurrently.

Ketoconazole

Dose reduction of indinavir to 600 mg every 8 hours is recommended when administering ketoconazole concurrently.

Rifabutin

Dose reduction of rifabutin to half the standard dose (consult the manufacturer's product circular for rifabutin - three 333-mg capsules) and a dose increase of indinavir to 1000 mg every 8 hours are recommended when rifabutin and indinavir are coadministered.

Hepatic Insufficiency

The dosage of indinavir should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis.

Nephrolithiasis/Urolithiasis

In addition to adequate hydration, medical management in patients who experience nephrolithiasis/urolithiasis may include temporary interruption (e.g. 1- 3 days) or discontinuation of therapy.

CONTRAINDICATIONS

INDIVAN is contraindicated in patients with clinically significant hypersensitivity to any of its components.

Inhibition of CYP3A4 by indinavir can result in elevated plasma concentrations of the following drugs, potentially causing serious or life-threatening reactions:

Table 2: Drug Interactions with Indinavir: Contraindicated Drugs

| Drug Class | Drugs Within Class That Are Contraindicated With Indinavir |
|----------------------------------|---|
| Alpha1-adrenoreceptor antagonist | alfuzosin |
| Antiarrhythmics | amiodarone |
| Ergot derivatives | dihydroergotamine, ergonovine, ergotamine, methylergonovine |
| Sedative/hypnotics | oral midazolam, triazolam, alprazolam |
| GI motility agents | cisapride |
| Neuroleptics | pimozide |
| PDE5 inhibitors | sildenafil (for treatment of pulmonary arterial hypertension) |

WARNINGS AND PRECAUTIONS

ALERT: Find out about medicines that should NOT be taken with INDIVAN.

Nephrolithiasis/Urolithiasis

Nephrolithiasis/urolithiasis has occurred with indinavir therapy. The cumulative frequency of nephrolithiasis is substantially higher in paediatric patients (29%) than in adult patients (12.4%; range across individual trials: 4.7% to 34.4%). The cumulative frequency of nephrolithiasis events increases with increasing exposure to indinavir; however, the risk over time remains relatively constant. In some cases, nephrolithiasis/urolithiasis has been associated with renal insufficiency or acute renal failure, pyelonephritis with or without bacteraemia. If signs or symptoms of nephrolithiasis/urolithiasis occur (including flank pain, with or without hematuria or microscopic hematuria), temporary interruption (e.g. 1-3 days) or discontinuation of therapy may be considered. **Adequate hydration is recommended in all patients treated with indinavir.** (see **UNDESIRABLE EFFECTS** and **DOSAGE AND ADMINISTRATION, Nephrolithiasis and Urolithiasis**)

Hemolytic Anemia

Acute haemolytic anemia, including cases resulting in death, has been reported in patients treated with indinavir. Once a diagnosis is apparent, appropriate measures for the treatment of haemolytic anemia should be instituted, including discontinuation of indinavir.

Hepatitis

Hepatitis including cases resulting in hepatic failure and death has been reported in patients treated with indinavir. Because the majority of these patients had confounding medical conditions and/or were receiving concomitant therapies, a causal relationship between indinavir and these events has not been established.

Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycaemic agents for the treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycaemia persisted in some cases. Because these events have been reported voluntarily, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

General

Indirect hyperbilirubinemia has occurred frequently during treatment with indinavir and has infrequently been associated with increases in serum transaminases (see also **UNDESIRABLE EFFECTS; Post-Marketing Experience**). It is not known whether indinavir will exacerbate the physiologic hyperbilirubinemia seen in neonates. (see **PREGNANCY**)

Tubulointerstitial Nephritis

Reports of tubulointerstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leukocyturia (>100 cells/high power field). Patients with asymptomatic severe leukocyturia should be followed closely and monitored frequently with urinalyses. Further diagnostic evaluation may be warranted, and discontinuation of **INDIVAN** should be considered in all patients with severe leukocyturia.

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including indinavir. During the initial phase of treatment, patients responding to antiretroviral therapy whose immune system responds to CART may develop an inflammatory response to indolent or residual opportunistic infections (such as MAI, CMV, PCP, or TB), which may necessitate further evaluation and treatment.

Coexisting Conditions

Patients with haemophilia: There have been reports of spontaneous bleeding in patients with haemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established. (see **UNDESIRABLE EFFECTS; Post-Marketing Experience**)

Patients with hepatic insufficiency due to cirrhosis: In these patients, the dosage of indinavir should be lowered because of decreased metabolism of indinavir (see **DOSAGE AND ADMINISTRATION**).

Patients with renal insufficiency: Patients with renal insufficiency have not been studied.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral 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.

Drug Interactions

Concomitant use of indinavir with lovastatin or simvastatin or rosuvastatin is not recommended.

Caution should be exercised if HIV protease inhibitors, including indinavir, are used concurrently with atorvastatin. The risk of myopathy including rhabdomyolysis may be

increased when HIV protease inhibitors, including indinavir, are used in combination with these statin drugs.

Midazolam is extensively metabolized by CYP3A4. Co-administration with indinavir with or without ritonavir may cause a large increase in the concentration of this benzodiazepine. No drug interaction study has been performed for the co-administration of indinavir with benzodiazepines. Based on data from other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally.

Therefore **INDIVAN** should not be co-administered with orally administered midazolam (see **CONTRAINDICATIONS**), whereas caution should be used with co-administration of **INDIVAN** 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 **INDIVAN** with or without ritonavir is co-administered with parenteral midazolam, it should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered.

Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving indinavir. Co-administration of indinavir with these medications is expected to substantially increase plasma concentrations of sildenafil, tadalafil, and vardenafil and may result in an increase in adverse events, including hypotension, visual changes, and priapism, which have been associated with sildenafil, tadalafil, and vardenafil.

Concomitant use of indinavir and St. John's wort (*Hypericum perforatum*) or products containing

St. John's wort is not recommended. Co-administration of indinavir and St. John's wort has been shown to substantially decrease indinavir concentrations and may lead to loss of virologic response and possible resistance to indinavir or to the class of protease inhibitors.

Indinavir is an inhibitor of the cytochrome P450 isoform CYP3A4. Co-administration of indinavir and drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

Indinavir is metabolized by CYP3A4. Drugs that induce CYP3A4 activity would be expected to increase the clearance of indinavir, resulting in lowered plasma concentrations of indinavir.

Co administration of indinavir and other drugs that inhibit CYP3A4 may decrease the clearance of indinavir and may result in increased plasma concentrations of indinavir.

Table 3: Drugs That Should Not be Co-administered with INDINAVIR

| Drug Class: Drug Name | Clinical Comment |
|--|---|
| Alpha 1-adrenoreceptor antagonist: Alfuzosin | Potentially increased alfuzosin concentrations can result in hypotension. |
| Antiarrhythmics: amiodarone | CONTRAINDICATED due to potential for serious and/or life threatening reactions such as cardiac arrhythmias. |
| Ergot derivatives: dihydroergotamine, Ergonovine, ergotamine, methylergonovine | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischaemia of the extremities and other tissues. |
| Sedative/hypnotics: midazolam, triazolam, alprazolam | CONTRAINDICATED due to potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression. |
| GI motility agents: cisapride | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |
| Neuroleptic: pimozide | CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias. |
| Herbal products: St. John`s wort (<i>Hypericum perforatum</i>) | May lead to loss of virologic response and possible resistance to indinavir or to the class of protease inhibitors. |

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| Antimycobacterial: rifampin | May lead to loss of virologic response and possible resistance to indinavir or to the class of protease inhibitors or other co administered antiretroviral agents. |
| HMG-CoA Reductase inhibitors: lovastatin, simvastatin and rosuvastatin | Potential for serious reactions such as risk of myopathy including rhabdomyolysis. |
| Protease inhibitor: atazanavir | Both indinavir and atazanavir are associated with indirect (unconjugated) hyperbilirubinaemia. Combinations of these drugs have not been studied and coadministration of indinavir and atazanavir is not recommended. |
| PDE5 inhibitor: sildenafil (for treatment of pulmonary arterial hypertension) | A safe and effective dose has not been established when used with indinavir. There is increased potential for sildenafil-associated undesirable effects (which include visual disturbances, hypotension, prolonged erection and syncope) |

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction (See Warnings and Precautions and Dosage and Administration)

| Drug Name | Effect | Clinical Comment |
|-----------------------------|---------------------------|---|
| HIV Antiviral Agents | | |
| Delavirdine | ↑ indinavir concentration | Dose reduction of INDIVAN to 600 mg every 8 hours should be considered when taking delavirdine 400 mg three times a day. |
| Didanosine | | Indinavir and didanosine formulations containing buffer should be administered at least one hour apart on an empty stomach |

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| Efavirenz | ↓ indinavir concentration | The optimal dose of INDIVAN , when given in combination with efavirenz, is not known. Increasing the indinavir dose to 1000 mg every 8 hours does not compensate for the increased indinavir metabolism due to efavirenz. |
| Nelfinavir | ↑ indinavir concentration | The appropriate doses for this combination, with respect to efficacy and safety, have not been established. |
| Nevirapine | ↓ indinavir concentration | Indinavir concentrations may be decreased in the presence of nevirapine. The appropriate doses for this combination, with respect to efficacy and safety, have not been established. |
| Ritonavir | ↑ indinavir concentration ↑ ritonavir concentration | The appropriate doses for this combination, with respect to efficacy and safety, have not been established. Preliminary clinical data suggest that the incidence of nephrolithiasis is higher in patients receiving indinavir in combination with ritonavir than those receiving Indinavir 800 mg q8h. |
| Saquinavir | ↑ Saquinavir concentration | The appropriate doses for this combination, with respect to efficacy and safety, have not been established. |
| Other Agents | | |
| Antiarrhythmics: bepridil, lidocaine (systemic) and quinidine | ↑ antiarrhythmic agents concentration | Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with INDIVAN |
| Anticonvulsants: carbamazepine, Phenobarbital, phenytoin | ↓ indinavir concentration | Use with caution, INDIVAN may not be effective due to decreased indinavir concentrations in patients taking these agents concomitantly. |

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| <p>Anti-gout: Colchicine</p> | <p>↑ colchicine concentration</p> | <p>Patients with renal or hepatic impairment should not be given colchicine with Indinavir.</p> <p>Treatment of gout flares: Co-administration of colchicine in patients on Indinavir: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Dose to be repeated no earlier than 3 days.</p> <p>Prophylaxis of gout flares: Co-administration of colchicine in patients on Indinavir : If the original colchicine regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original colchicine regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day.</p> <p>Treatment of familial Mediterranean fever (FMF): Co-administration of colchicine in patients on Indinavir : Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).</p> |
| <p>Calcium Channel Blockers, Dihydropyridine: e.g., felodipine, nifedipine, nicardipine</p> | <p>↑ dihydropyridine calcium channel blockers concentration</p> | <p>Caution is warranted and clinical monitoring of patients is recommended.</p> |
| <p>Clarithromycin</p> | <p>↑ clarithromycin concentration ↑ indinavir concentration</p> | <p>The appropriate doses for this combination, with respect to efficacy and safety, have not been established.</p> |
| <p>Endothelin receptor antagonist: Bosentan</p> | <p>↑ bosentan concentration</p> | <p>Co-administration of bosentan in patients on Indinavir or coadministration of Indinavir in patients on bosentan: Start at or adjust bosentan to 62.5 mg once daily or every other day based upon individual tolerability.</p> |

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| Inhaled/nasal steroid: Fluticasone | ↑ fluticasone concentration | Concomitant use of fluticasone propionate and indinavir may increase plasma concentrations of fluticasone propionate. Use with caution. Consider alternatives to fluticasone propionate, particularly for long-term use. Fluticasone use is not recommended in situations where indinavir is coadministered with a potent CYP3A4 inhibitor such as ritonavir unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects. |
| HMG-CoA Reductase inhibitor: atorvastatin, pravastatin, fluvastatin | ↑ atorvastatin concentration pravastatin, fluvastatin interaction not studied | Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring. If no alternative treatment is available, use with careful monitoring. |
| Immunosuppressants: cyclosporine, tacrolimus, sirolimus | ↑ immunosuppressant agents concentration | Plasma concentrations may be increased by indinavir. |
| Itraconazole | ↑ indinavir concentration | Dose reduction of indinavir to 600 mg every 8 hours is recommended when administering itraconazole concurrently |
| Midazolam (parenteral administration) | ↑ midazolam concentration | Concomitant use of parenteral midazolam with indinavir may increase plasma concentrations of midazolam. Coadministration should be done in a setting which |

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| | | <p>ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of oral midazolam with indinavir is CONTRAINDICATED (see Table 3).</p> |
| Ketoconazole | ↑ indinavir concentration | Dose reduction of INDIVAN to 600 mg every 8 hours should be considered |
| Rifabutin | ↓ indinavir concentration ↑ rifabutin concentration | Dose reduction of rifabutin to half the standard dose and a dose increase of indinavir to 1000 mg (three 333-mg capsules) every 8 hours are recommended when rifabutin and indinavir are coadministered |
| Sildenafil | ↑ sildenafil concentration (only the use of sildenafil at doses used for treatment of erectile dysfunction has been studied with indinavir) | <p>May result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances, and priapism.</p> <p><i>Use of sildenafil for pulmonary arterial hypertension (PAH):</i> Use of Revatio1 (sildenafil) is contraindicated when used for the treatment of pulmonary arterial hypertension (PAH) (see CONTRAINDICATIONS).</p> <p><i>Use of sildenafil for erectile dysfunction:</i> Sildenafil dose should not exceed a maximum of 25 mg in a 48hour period in patients</p> |

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| | | receiving concomitant therapy. Use with increased monitoring for adverse events. |
| Tadalafil | ↑ tadalafil concentration | <p>May result in an increase in PDE5 inhibitor-associated adverse events, including hypotension, visual disturbances, and priapism.</p> <p><i>Use of tadalafil for pulmonary arterial hypertension (PAH):</i> The following dose adjustments are recommended for use of tadalafil with INDIVAN: Co-administration of tadalafil in patients on INDIVAN or co-administration of INDIVAN in patients on tadalafil: Start at or adjust tadalafil to 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability.</p> <p><i>Use of tadalafil for erectile dysfunction:</i> Tadalafil dose should not exceed a maximum of 10 mg in a 72hour period in patients receiving concomitant INDIVAN therapy. Use with increased monitoring for adverse events.</p> |
| Antidepressant: Trazodone | ↑ Trazodone concentration | <p>Concomitant use of trazodone and INDIVAN may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as INDIVAN, the combination should be used with caution and a lower dose of trazodone should be</p> |

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| | | considered. |
| Vardenafil | ↑ vardenafil concentration | Vardenafil dose should not exceed a maximum of 2.5 mg in a 24-hour period in patients receiving concomitant indinavir therapy. |
| Venlafaxine | ↓ Indinavir concentration | In a study of 9 healthy volunteers, venlafaxine administered under steady-state conditions at 150 mg/day resulted in a 28% decrease in the AUC of a single 800 mg oral dose of indinavir and a 36% decrease in indinavir C _{max} . Indinavir did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of this finding is unknown. |
| Note: = ↑increase; ↓ = decrease | | |

Pregnancy

Pregnancy Category C

Developmental toxicity studies were performed in rabbits (at doses up to 240 mg/kg/day), dogs (at doses up to 80 mg/kg/day), and rats (at doses up to 640 mg/kg/day). The highest doses in these studies produced systemic exposures in these species comparable to or slightly greater than human exposure. No treatment-related external, visceral, or skeletal changes were observed in rabbits or dogs. No treatment-related external or visceral changes were observed in rats. Treatment-related increases over controls in the incidence of supernumerary ribs (at exposures at or below those in humans) and of cervical ribs (at exposures comparable to or slightly greater than those in humans) were seen in rats. In all three species, no treatment-related effects on embryonic/fetal survival or fetal weights were observed.

In rabbits, at a maternal dose of 240 mg/kg/day, no drug was detected in fetal plasma 1 hour after dosing. Fetal plasma drug levels 2 hours after dosing were approximately 3% of maternal plasma drug levels. In dogs, at a maternal dose of 80 mg/kg/day, fetal plasma drug levels were approximately 50% of maternal plasma drug levels both 1 and 2 hours after dosing. In rats, at maternal doses of 40 and 640 mg/kg/day, fetal

plasma drug levels were approximately 10 to 15% and 10 to 20% of maternal plasma drug levels 1 and 2 hours after dosing, respectively.

Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately fourfold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy.

In Rhesus monkeys, fetal plasma drug levels were approximately 1 to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

Hyperbilirubinemia has occurred during treatment with indinavir (see **UNDESIRABLE EFFECTS**). It is unknown whether indinavir administered to the mother in the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates.

There are no adequate and well-controlled studies in pregnant patients. **INDIVAN** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Indinavir dose of 800 mg every 8 hours (with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day) has been studied in 16 HIV-infected pregnant patients at 14 to 28 weeks of gestation at enrollment (study PACTG 358). Given the substantially lower antepartum exposures observed and the limited data in this patient population, indinavir use is not recommended in HIV-infected pregnant patients.

Lactation

Studies in lactating rats have demonstrated that indinavir is excreted in milk. Although it is not known whether indinavir is excreted in human milk, there exists the potential for adverse effects from indinavir in nursing infants. **Mothers should be instructed to discontinue nursing if they are receiving INDIVAN.** It is also recommended that HIV-infected mothers not breastfeed their infants to avoid risking post-natal transmission of HIV. Prevention that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use

The optimal dosing regimen for use of indinavir in paediatric patients has not been established. A dose of 500 mg/m² every eight hours has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles previously observed in adults receiving the recommended dose (see **PHARMACOLOGY**, Pediatric). Although viral suppression was observed in some of the 32 children who were followed on this regimen through 24 weeks, a substantially higher rate of nephrolithiasis was reported when compared to adult historical data (see **WARNINGS AND PRECAUTIONS**, Nephrolithiasis/Urolithiasis). Physicians considering the use of indinavir in pediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

UNDESIRABLE EFFECTS

Clinical Trials in Adults

Nephrolithiasis/urolithiasis, including flank pain with or without haematuria (including microscopic hematuria), has been reported in approximately 12.4% (301/2429; range across individual trials: 4.7% to 34.4%) of patients receiving indinavir at the recommended dose in clinical trials with a median follow-up of 47 weeks (range: 1 day to 242 weeks; 2238 patient-years follow-up). The cumulative frequency of nephrolithiasis events increases with duration of exposure to indinavir; however, the risk over time remains relatively constant. Of the patients treated with indinavir who developed nephrolithiasis/urolithiasis in clinical trials during the double-blind phase, 2.8% (7/246) were reported to develop hydronephrosis and 4.5% (11/246) underwent stent placement.

Following the acute episode, 4.9% (12/246) of patients discontinued therapy. (see **WARNINGS and DOSAGE AND ADMINISTRATION; Nephrolithiasis/Urolithiasis.**)

Asymptomatic hyperbilirubinaemia (total bilirubin \geq 2.5 mg/dl), reported predominantly as elevated indirect bilirubin, has occurred in approximately 14% of patients treated with indinavir. In <1 % this was associated with elevations in AST or ALT.

Hyperbilirubinaemia and nephrolithiasis/urolithiasis occurred more frequently at doses exceeding 2.4 g/day compared to doses \leq 2.4 g/day.

Clinical adverse experiences reported in \geq 2% of patients treated with indinavir alone, indinavir in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 5.

Table 5: Clinical Adverse Experiences Reported in \geq 2% of Patients

| | Study 028 Considered Drug-Related and of Moderate or Severe Intensity | Study ACTG 320 of Unknown Drug Relationship and of Severe or Life- threatening Intensity |
|--|--|---|
| | | |

| | Indinavr | Indinavir plus Zidovudine | Zidovudine | Indinavir plus Zidovudine plus Lamivudine | Zidovudine plus Lamivudine |
|--|-----------------|---------------------------|-----------------|---|----------------------------|
| Adverse Experience | Percent (n=332) | Percent (n=332) | Percent (n=332) | Percent (n=571) | Percent (n=575) |
| <i>Body as a whole</i> | | | | | |
| Abdominal pain | 16.6 | 16.0 | 12.0 | 1.9 | 0.7 |
| Asthenia/fatigue | 2.1 | 4.2 | 3.6 | 2.4 | 4.5 |
| Fever | 1.5 | 1.5 | 2.1 | 3.8 | 3.0 |
| Malaise | 2.1 | 2.7 | 1.8 | 0 | 0 |
| <i>Digestive system</i> | | | | | |
| Nausea | 11.7 | 31.9 | 19.6 | 2.8 | 1.4 |
| Diarrhea | 3.3 | 3.0 | 2.4 | 0.9 | 1.2 |
| Vomiting | 8.4 | 17.8 | 9.0 | 1.4 | 1.4 |
| Acid regurgitation | 2.7 | 5.4 | 1.8 | 0.4 | 0 |
| Anorexia | 2.7 | 5.4 | 3.0 | 0.5 | 0.2 |
| Apettite increase | 2.1 | 1.5 | 1.2 | 0 | 0 |
| Dyspepsia | 1.5 | 2.7 | 0.9 | 0 | 0 |
| Jaundice | 1.5 | 2.1 | 0.3 | 0 | 0 |
| <i>Hemic and Lymphatic System</i> | | | | | |
| Anemia | 0.6 | 1.2 | 2.1 | 2.4 | 3.5 |
| <i>Musculoskeletal System</i> | | | | | |
| Back pain | 8.4 | 4.5 | 1.5 | 0.9 | 0.7 |
| <i>Nervous System/Psychiatric</i> | | | | | |
| Headache | 5.4 | 9.6 | 6.0 | 2.4 | 2.8 |
| Dizziness | 3.0 | 3.9 | 0.9 | 0.5 | 0.7 |
| Somnolence | 2.4 | 3.3 | 3.3 | 0 | 0 |
| <i>Skin and skin Appendage</i> | | | | | |
| Pruritis | 4.2 | 2.4 | 1.8 | 0.5 | 0 |
| Rash | 1.2 | 0.6 | 2.4 | 1.1 | 0.5 |
| <i>Respiratory System</i> | | | | | |
| Cough | 1.5 | 0.3 | 0.6 | 1.6 | 1.0 |
| Difficulty breathing/dyspnea shortness of breath | 0 | 0.6 | 0.3 | 1.8 | 1.0 |
| <i>Urogenital System</i> | | | | | |
| Nephrolithiasis/uroolithiasis* | 8.7 | 7.8 | 2.1 | 2.6 | 0.3 |
| Dysuria | 1.5 | 2.4 | 0.3 | 0.4 | 0.2 |
| <i>Special Senses</i> | | | | | |

| | | | | | |
|------------------|-----|-----|-----|-----|---|
| Taste perversion | 2.7 | 8.4 | 1.2 | 0.2 | 0 |
|------------------|-----|-----|-----|-----|---|

*Including renal colic, and flank pain with and without hematuria

In Phase I and II controlled trials, the following adverse events were reported significantly more frequently by those randomized to the arms containing indinavir than by those randomized to nucleoside analogues: rash, upper respiratory infection, dry skin, pharyngitis, taste perversion.

Selected laboratory abnormalities of severe or life-threatening intensity reported in patients treated with indinavir alone, Indinavir in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 6.

Table 6: Selected Laboratory Abnormalities of Severe or Life-threatening Intensity Reported in Studies 028 and ACTG 320

| | Study 028 | | | Study ACTG 320 | |
|--|-----------------|---------------------------|-----------------|---|----------------------------|
| | Indinavir | Indinavir plus Zidovudine | Zidovudine | Indinavir plus Zidovudine plus Lamivudine | Zidovudine plus Lamivudine |
| | Percent (n=329) | Percent (n=320) | Percent (n=330) | Percent (n=571) | Percent (n=575) |
| <i>Hematology</i> | | | | | |
| Decreased hemoglobin <7.0 g/dL | 0.6 | 0.9 | 3.3 | 2.4 | 3.5 |
| Decreased platelet count <50 THS/mm ³ | 0.9 | 0.9 | 1.8 | 0.2 | 0.9 |
| Decreased neutrophils <0.75 THS/mm ³ | 2.4 | 2.2 | 6.7 | 5.1 | 14.6 |
| <i>Blood chemistry</i> | | | | | |

| | | | | | |
|---|------|-----|-----|-----|-----|
| Increased ALT >500% ULN * | 4.9 | 4.1 | 3.0 | 2.6 | 2.6 |
| Increased AST >500% ULN | 3.7 | 2.8 | 2.7 | 3.3 | 2.8 |
| Total serum bilirubin >250% ULN | 11.9 | 9.7 | 0.6 | 6.1 | 1.4 |
| Increased serum amylase >200% ULN | 2.1 | 1.9 | 1.8 | 0.9 | 0.3 |
| Increased glucose >250 mg/dL | 0.9 | 0.9 | 0.6 | 1.6 | 1.9 |
| Increased creatinine >300% ULN | 0 | 0 | 0.6 | 0.2 | 0 |
| *Upper limit of the normal range. | | | | | |

Post-marketing experience

Body as a Whole: Redistribution/accumulation of body fat. (see **WARNINGS AND PRECAUTIONS**)

Cardiovascular System: Cardiovascular disorders including myocardial infarction and angina pectoris; cerebrovascular disorder

Digestive System: Liver function abnormalities, hepatitis including reports of hepatic failure, pancreatitis, jaundice, abdominal distention, dyspepsia (see **WARNINGS AND PRECAUTIONS**); pancreatitis; jaundice; abdominal distention; dyspepsia.

Haematologic: Increased spontaneous bleeding in patients with haemophilia (see

WARNINGS AND PRECAUTIONS); acute hemolytic anaemia (see **WARNINGS AND PRECAUTIONS**).

Endocrine/Metabolic: New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycaemia (see **WARNINGS AND PRECAUTIONS**)

Hypersensitivity: Anaphylactoid reactions; urticaria; vasculitis

Musculoskeletal System: Arthralgia

Nervous System / Psychiatric: Oral paraesthesia; depression

Skin and Skin Appendages: Rash including erythema multiforme and Stevens-Johnson Syndrome; hyperpigmentation: alopecia; ingrown toenails and/or paronychia; pruritus.

Urogenital System: Nephrolithiasis/urolithiasis; in some cases resulting in renal insufficiency or acute renal failure; pyelonephritis with or without bacteremia (see **WARNINGS AND PRECAUTIONS**) interstitial nephritis sometimes with indinavir crystal deposits; in some patients, the interstitial nephritis did not resolve following discontinuation of indinavir; renal failure, leukocyturia (see **WARNINGS AND PRECAUTIONS**) crystalluria; dysuria.

Laboratory abnormalities: Increased serum triglycerides, increased serum cholesterol

OVERDOSAGE

There have been more than 60 reports of acute or chronic human overdose (up to 23 times the recommended total daily dose of 2400 mg) with indinavir. The most commonly reported symptoms were renal (e.g., nephrolithiasis/urolithiasis, flank pain, haematuria) and gastrointestinal (e.g., nausea, vomiting, diarrhoea). It is not known whether indinavir is dialysable by peritoneal or haemodialysis.

PACKAGING INFORMATION

INDIVAN - 400..... Container of 30 capsules

Last updated: October 2010