**Presentation**

ARROW - EFAVIRENZ is a yellow coloured, film coated, oval shaped tablet debossed with “EF 600” on one side and plain on the other side.

**Uses**

**Actions**

ARROW - EFAVIRENZ is a selective non-nucleoside reverse transcriptase inhibitor of human immunodeficiency virus type 1 (HIV-1).

ARROW - EFAVIRENZ is a non-competitive inhibitor of HIV-1 reverse transcriptase (RT) with respect to template, primer or nucleoside triphosphates, with a small component of competitive inhibition. HIV-2 RT and human cellular DNA polymerases α, β, γ and δ are not inhibited by concentrations of ARROW - EFAVIRENZ well in excess of those achieved clinically.

**Pharmacokinetics**

**Absorption**

Peak efavirenz plasma concentrations of 1.6-9.1 µM were attained by 5 hours following single oral doses of 100 mg to 1600 mg administered to uninfected volunteers. Dose-related increases in Cmax and AUC were seen for doses up to 1600 mg; the increases were less than proportional suggesting diminished absorption at higher doses. Time to peak plasma concentrations (3-5 hours) did not change following multiple dosing and steady-state plasma concentrations were reached in 6-7 days.

In HIV-infected patients at steady state, mean Cmax, mean Cmin, and mean AUC were linear with 200 mg, 400 mg, and 600 mg daily doses. In 35 patients receiving efavirenz 600 mg once daily, steady-state Cmax was 12.9 µM, steady-state Cmin was 5.6 µM, and AUC was 184 µM•h.

**Effect of Food on Oral Absorption:**

The bioavailability of a single 600 mg dose of efavirenz in uninfected volunteers was increased 22% and 17%, respectively, when given with a meal of high fat or normal composition, relative to the bioavailability of a 600 mg dose given under fasted conditions.

ARROW - EFAVIRENZ can be administered with or without food.
Distribution

Efavirenz is highly bound (approximately 99.5-99.75%) to human plasma proteins, predominantly albumin. In HIV-1 infected patients (N=9) who received efavirenz 200 to 600 mg once daily for at least one month, cerebrospinal fluid concentrations ranged from 0.26 to 1.19% (mean 0.69%) of the corresponding plasma concentration. This proportion is approximately 3-fold higher than the non-protein-bound (free) fraction of efavirenz in plasma.

Metabolism

Studies in humans and in vitro studies using human liver microsomes have demonstrated that efavirenz is principally metabolised by the cytochrome P450 system to hydroxylated metabolites with subsequent glucuronidation of these hydroxylated metabolites. These metabolites are essentially inactive against HIV-1. The in vitro studies suggest that CYP3A4 and CYP2B6 are the major isozymes responsible for efavirenz metabolism.

In vitro studies have shown that efavirenz inhibited P450 isozymes 2C9, 2C19, and 3A4 with Ki values (8.5-17µM) in the range of observed efavirenz plasma concentrations. In in vitro studies, efavirenz did not inhibit CYP2E1 and inhibited CYP2D6 and CYP1A2 (Ki values 82-160 µM) only at concentrations well above those achieved clinically.

Efavirenz plasma exposure may be increased in patients with the homozygous G516T genetic variant of the CYP2B6 isoenzyme. The clinical implications of such an association are unknown; however, the potential for an increased frequency and severity of efavirenz-associated adverse events cannot be excluded.

Efavirenz has been shown to induce P450 enzymes, resulting in the induction of its own metabolism. Multiple doses of 200-400 mg per day for 10 days resulted in a lower than predicted extent of accumulation (22-42% lower) and a shorter terminal half-life of 40-55 hours (single dose half-life 52-76 hours). The degree of CYP3A4 induction is expected to be similar between a 400 mg and 600 mg dose of efavirenz based on pharmacokinetic interaction studies in which daily 400 mg or 600 mg efavirenz doses in combination with indinavir did not appear to cause any further reduction of indinavir AUC compared to a 200 mg dose of efavirenz.

Elimination

Efavirenz has a relatively long terminal half-life of 52 to 76 hours after single doses and 40-55 hours after multiple doses. Approximately 14-34% of a radiolabelled dose of efavirenz was recovered in the urine and less than 1% of the dose was excreted in urine as unchanged efavirenz.

Characteristics in Patients

Hepatic Impairment

The pharmacokinetics of efavirenz have not been adequately studied in patients with hepatic impairment (see Warnings and Precautions).
Renal Impairment

The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency; however, less than 1% of efavirenz is excreted unchanged in the urine, so the impact of renal impairment on ARROW - EFAVIRENZ elimination should be minimal.

Gender and Race

Pharmacokinetics of efavirenz in patients appear to be similar between men and women and among the racial groups studied.

Geriatric Use

Clinical studies of efavirenz did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Paediatric Use

Efavirenz has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg. In a clinical trial of 57 paediatric patients, the type and frequency of adverse experiences was generally similar to that of adult patients with the exception of a higher incidence of new-onset rash in children (46%). (See Adverse Effects).

The pharmacokinetics of efavirenz in paediatric patients were similar to adults. In 48 paediatric patients receiving the equivalent of a 600 mg dose of efavirenz (dose adjusted from calculated body size based on weight), steady-state Cmax was 14.2 µM, steady-state Cmin was 5.6 µM, and AUC was 218 µM•h.

Indications

ARROW - EFAVIRENZ is indicated in antiviral combination treatment of HIV-1 infected adults, adolescents and children.

Dosage and Administration

Adults

The recommended dosage of ARROW - EFAVIRENZ in combination with a protease inhibitor and/or nucleoside analogue reverse transcriptase inhibitors (NRTIs) is 600 mg orally, once daily.

ARROW - EFAVIRENZ may be taken with or without food, as desired.

In order to improve the tolerability of nervous system side effects, bedtime dosing is recommended during the first two to four weeks of therapy and in patients who continue to experience these symptoms (see Adverse Effects).

Concomitant Antiretroviral Therapy: ARROW - EFAVIRENZ must be given in combination with other antiretroviral medications (see Interactions).
Adolescents and children (17 years and under)

The recommended dose of ARROW - EFAVIRENZ in combination with a protease inhibitor and/or NRTIs for patients 17 years of age and under is described in Table 1. ARROW - EFAVIRENZ tablets should only be administered to children who are able to reliably swallow tablets.

ARROW - EFAVIRENZ may be taken with or without food, as desired.

ARROW - EFAVIRENZ has not been adequately studied in children under the age of 3 years or children weighing less than 13 kg.

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<thead>
<tr>
<th>Body Weight (kg)</th>
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<td>13 to &lt;15</td>
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Contraindications

ARROW - EFAVIRENZ is contraindicated in patients with clinically significant hypersensitivity to any of its components.

ARROW - EFAVIRENZ should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozide, bepridil, or ergot derivatives because competition for CYP3A4 by ARROW - EFAVIRENZ could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events e.g., cardiac arrhythmias, prolonged sedation or respiratory depression.

ARROW - EFAVIRENZ is contraindicated in pregnancy (see Warnings and Precautions).

ARROW - EFAVIRENZ must not be administered concurrently with the standard doses of voriconazole because ARROW - EFAVIRENZ significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases ARROW - EFAVIRENZ plasma concentrations (see Interactions; for use of adjusted doses of voriconazole with adjusted doses of efavirenz, see Interactions).
Warnings and Precautions

ARROW - EFAVIRENZ must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen.

When prescribing medicines concomitantly with ARROW - EFAVIRENZ, physicians should refer to the corresponding manufacturer’s data sheet.

If any antiretroviral medication in a combination regimen is interrupted because of suspected intolerance, serious consideration should be given to simultaneous discontinuation of all antiretroviral medications. The antiretroviral medications should be restarted at the same time upon resolution of the intolerance symptoms. Intermittent monotherapy and sequential reintroduction of antiretroviral agents is not advisable because of the increased potential for selection of medicine-resistant mutant virus.

Co-administration of ARROW - EFAVIRENZ with combination products that contain efavirenz is not recommended.

Malformations have been observed in foetuses from ARROW - EFAVIRENZ-treated animals (see Warnings and Precautions, Pregnancy); therefore, pregnancy should be avoided in women receiving ARROW - EFAVIRENZ. (See Contraindications.) Barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives) (see Warnings and Precautions, Pregnancy and Interactions).

Skin Rash

Mild-to-moderate rash has been reported in clinical trials with efavirenz and usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve the tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was 0.14%.

ARROW - EFAVIRENZ should be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Efavirenz is not recommended for patients who have had a life-threatening cutaneous reaction (e.g. Stevens-Johnson syndrome). If therapy with ARROW - EFAVIRENZ is discontinued, consideration should also be given to interrupting therapy with other anti-retroviral agents to avoid development of medicine resistant virus (see Adverse Effects).

Rash was reported in 26 of 57 children (46%) treated with efavirenz and was severe in 3 patients (5%). Prophylaxis with appropriate antihistamines prior to initiating therapy with ARROW - EFAVIRENZ in children may be considered.

Psychiatric symptoms

Psychiatric adverse experiences have been reported in patients treated with efavirenz. Patients with a history of psychiatric disorders appear to be at greater risk
of these serious psychiatric adverse experiences. There have also been post-marketing reports of death by suicide, delusions and psychosis-like behaviour, although a causal relationship to the use of ARROW - EFAVIRENZ cannot be determined from these reports.

Patients should be advised that if they experience these symptoms they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of ARROW - EFAVIRENZ, and if so, to determine whether the risks of continued therapy outweigh the benefits (see Adverse Effects).

**Nervous system symptoms**

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration and abnormal dreaming are frequently reported undesirable effects in patients receiving efavirenz 600 mg daily in clinical studies (see Adverse Effects). Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.

**Seizures**

Convulsions have been observed rarely in patients receiving efavirenz, generally in the presence of known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolised by the liver, such as phenytoin, carbamazepine and phenobarbital, may require periodic monitoring of plasma levels. In a medicine interaction study, carbamazepine plasma concentrations were decreased when carbamazepine was co-administered with efavirenz (see Interactions).

Caution must be taken in any patient with a history of seizures.

**Effect of food**

The administration of ARROW - EFAVIRENZ with food may increase ARROW - EFAVIRENZ exposure and may lead to an increase in the frequency of undesirable effects. Taking ARROW - EFAVIRENZ on an empty stomach, preferably at bedtime, can be considered.

**Immune Reconstitution Syndrome**

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (CART), including efavirenz.

During the initial phase of treatment, a patient whose immune system responds to CART may mount an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

**Special Populations**

Efavirenz is not recommended for patients with moderate or severe hepatic impairment because of insufficient data to determine whether dose adjustment is necessary. Because of the extensive cytochrome P450-mediated metabolism of
ARROW - EFAVIRENZ and limited clinical experience in patients with chronic liver disease, caution should be exercised in administering ARROW - EFAVIRENZ to patients with hepatic impairment.

Patients with underlying liver disease including chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse events. A few of the post-marketing reports of hepatic failure occurred in patients with no pre-existing hepatic disease or other identifiable risk factors. Liver enzyme monitoring should also be considered for patients without pre-existing hepatic dysfunction or other risk factors.

The pharmacokinetics of ARROW - EFAVIRENZ have not been studied in patients with renal insufficiency; however, less than 1% of a ARROW - EFAVIRENZ dose is excreted unchanged in the urine, so the impact of renal impairment on ARROW - EFAVIRENZ elimination should be minimal.

There is no experience in patients with severe renal failure and close safety monitoring is recommended in this population.

Insufficient numbers of elderly patients have been evaluated in clinical studies to determine whether they respond differently from younger patients.

ARROW - EFAVIRENZ has not been evaluated in children below 3 years of age or who weigh less than 13 kg.

Liver Enzymes

In patients with known or suspected history of Hepatitis B or C infection and in patients treated with other medications associated with liver toxicity monitoring of liver enzymes is recommended.

In patients with persistent elevations of serum transaminases to greater than 5 times the upper limit of the normal range, the benefit of continued therapy with ARROW - EFAVIRENZ needs to be weighed against the unknown risks of significant liver toxicity. (See Adverse Effects.)

Paediatric Use

ARROW - EFAVIRENZ has not been studied in paediatric patients below 3 years of age or who weigh less than 13 kg.

Effects on the Ability to Drive and Use Machinery

ARROW - EFAVIRENZ may cause dizziness, impaired concentration, and/or drowsiness. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machinery.
Pregnancy and Lactation

Pregnancy

Pregnancy should be avoided in women treated with ARROW - EFAVIRENZ. Barrier contraception should always be used in combination with other methods of contraception (for example, oral or other hormonal contraceptives). Because of the long half-life of efavirenz, use of adequate contraceptive measures for 12 weeks after discontinuation of ARROW - EFAVIRENZ is recommended. Women of childbearing potential should undergo pregnancy testing before initiation of ARROW - EFAVIRENZ.

ARROW - EFAVIRENZ should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus and there are no other appropriate treatment options. If a woman takes ARROW - EFAVIRENZ during the first trimester of pregnancy or becomes pregnant while taking ARROW - EFAVIRENZ, she should be informed of the potential harm to the foetus.

There are no adequate and well-controlled studies of ARROW - EFAVIRENZ in pregnant women. In post-marketing experience through an antiretroviral pregnancy registry, more than 500 pregnancies with first-trimester exposure to efavirenz as part of a combination antiretroviral regimen have been reported with no specific malformation pattern. In this registry, a small number of cases of neural tube defects, including meningomyelocele, have been reported; most of these reports were retrospective, and causality has not been established.

Lactation

It is not known whether ARROW - EFAVIRENZ is excreted in human milk. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking ARROW - EFAVIRENZ do not breast-feed their infants. It is recommended that HIV-infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Animal Toxicology

Chronic Toxicity

Minimal to moderate biliary hyperplasia was observed in the livers of cynomolgus monkeys given efavirenz for 2 years at doses resulting in mean plasma AUC values approximately 2- or 9-fold greater than those in patients given 600 mg/day. One monkey with moderate biliary hyperplasia also had slight cholestasis. The biliary hyperplasia regressed upon cessation of dosing. At the end of the 2 year treatment period, 9/10 monkeys receiving the highest dose of efavirenz had minimal to moderate biliary hyperplasia. Following a 26-week treatment-free recovery period, 3/5 monkeys that had previously received the highest dose did not have biliary hyperplasia. The remaining two monkeys in the recovery group had minimal biliary hyperplasia.

Minimal to slight thyroid follicular cell hypertrophy occurred in cynomolgus monkeys given efavirenz for 2 years at doses resulting in mean plasma AUC values approximately 2- or 9-fold greater than those in patients given 600 mg/day. This
change resulted from increased thyroxine clearance secondary to hepatic enzyme induction. This finding is not judged to pose a risk to patients given efavirenz since chronic treatment with other known enzyme inducers is not associated with clinical hypothyroidism, goitre, or thyroid neoplasia.

Non-sustained convulsions were observed in cynomolgus monkeys receiving efavirenz for \( \geq 1 \) year, at doses yielding plasma efavirenz 4- to 13-fold greater than the plasma concentrations in humans given 600 mg/day. There were no efavirenz-related microscopic changes in the CNS of these monkeys.

**Carcinogenesis**

Carcinogenicity studies showed an increased incidence of hepatic and pulmonary tumours in female mice but not in male mice. There was no increase in the rate of any tumour in male mice or in male or female rats given efavirenz. The hepatic tumours are thought likely to be due to the enzyme-inducing effect of efavirenz; however, the cause of the increased pulmonary tumours and their relevance to humans is unknown.

**Mutagenesis**

Efavirenz was not mutagenic or genotoxic in in vitro and in vivo genotoxicity assays which included bacterial mutation assays in S. typhimurium and E. coli, mammalian mutation assays in Chinese Hamster Ovary cells, chromosomal aberration assays in human peripheral blood lymphocytes or Chinese Hamster Ovary cells, and an in vivo mouse bone marrow micronucleus assay.

**Reproduction**

Efavirenz did not impair mating or fertility of male or female rats, and did not affect sperm or offspring of treated male rats. The reproductive performance of offspring born to female rats given efavirenz was not affected. As a result of the rapid clearance of efavirenz in rats, systemic medicine exposures achieved at the doses used in these studies were equivalent to or below those achieved in humans given therapeutic doses of efavirenz.

**Development**

Malformations have been observed in 3 of 20 foetuses/newborns from efavirenz-treated cynomolgus monkeys in an ongoing developmental toxicity study. The pregnant monkeys were dosed with efavirenz 60 mg/kg/day, a dose resulting in plasma medicine concentrations similar to those in humans given 600 mg/day. Anencephaly and unilateral anophthalmia with secondary enlargement of the tongue were observed in one foetus, microophthalmia was observed in another foetus, and cleft palate was observed in a third foetus.

No malformations were observed in foetuses from efavirenz-treated rats; however, an increase in foetal resorptions was observed in rats given 200 mg/kg/day. The peak plasma concentrations and AUC values in pregnant female rats at this dose of efavirenz were equivalent to those achieved in humans given 600 mg of efavirenz once daily.
Efavirenz was not teratogenic or embryotoxic when given to pregnant rabbits at 75 mg/kg/day, a dose that produced peak plasma concentrations similar to, and AUC values approximately half of those achieved in humans given 600 mg of efavirenz once daily.

Efavirenz has been shown to cross the placenta in rats, rabbits, and cynomolgus monkeys. In these animals, foetal blood concentrations of efavirenz were similar to maternal efavirenz concentrations.

### Adverse Effects

Efavirenz was generally well tolerated in clinical trials. Efavirenz has been studied in over 9,000 patients. In a subset of 1,008 patients who received 600 mg efavirenz daily in combination with protease inhibitors and/or NRTIs in controlled clinical studies, the most frequently reported treatment-related undesirable effects of at least moderate severity reported in at least 5% of patients were rash (11.6%), dizziness (8.5%), nausea (8.0%), headache (5.7%) and fatigue (5.5%). Nausea was reported with a higher frequency in the control groups.

The most notable undesirable effects associated with efavirenz are rash, nervous system symptoms and psychiatric symptoms.

The administration of ARROW - EFAVIRENZ with food may increase ARROW - EFAVIRENZ exposure and may lead to an increase in the frequency of undesirable effects (see Warnings and Precautions).

Other, less frequent, clinically significant treatment-related undesirable effects reported in all clinical trials include: allergic reaction, abnormal co-ordination, ataxia, confusion, stupor, vertigo, vomiting, diarrhoea, hepatitis, impaired concentration, insomnia, anxiety, abnormal dreams, somnolence, depression, abnormal thinking, agitation, amnesia, delirium, emotional lability, euphoria, hallucination, and psychosis.

Additional undesirable effects reported in post-marketing surveillance include neurosis, paranoid reaction, cerebellar co-ordination and balance disturbances, convulsions, pruritus, abdominal pain, blurred vision, flushing, gynaecomastia, hepatic failure, photoallergic dermatitis, pancreatitis, redistribution/accumulation of body fat in areas such as the back of the neck, breasts, abdomen and retroperitoneum, tinnitus, and tremor.

A few of the post-marketing reports of hepatic failure, including cases in patients with no pre-existing hepatic disease or other identifiable risk factors, were characterised by a fulminant course, progressing in some cases to transplantation or death.

The type and frequency of undesirable effects in children was generally similar to that of adult patients with the exception that rash was reported more frequently in children and was more often of higher grade than in adults.
In clinical trials, 26% of patients treated with 600 mg of efavirenz experienced skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment-related in 18% of patients treated with efavirenz. Severe rash occurred in less than 1% of patients treated with efavirenz and 1.7% discontinued therapy because of rash. The incidence of erythema multiforme or Stevens-Johnson syndrome was 0.14%.

Rash was reported in 26 of 57 children (46%) treated with efavirenz and was severe in 3 patients (5%). Prophylaxis with appropriate antihistamines prior to initiating therapy with ARROW - EFAVIRENZ in children may be considered.

Rashes are usually mild-to-moderate maculopapular skin eruptions that occur within the first two weeks of initiating therapy with efavirenz. In most patients rash resolves with continuing therapy with efavirenz within one month. ARROW - EFAVIRENZ can be reinitiated in patients interrupting therapy because of rash. Use of appropriate antihistamines and/or corticosteroids is recommended when ARROW - EFAVIRENZ is restarted (see Warnings and Precautions).

Experience with efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. Nineteen patients who discontinued nevirapine because of rash have been treated with efavirenz. Nine of these patients developed mild-to-moderate rash while receiving therapy with efavirenz, and two discontinued because of rash.

Psychiatric Symptoms

Serious psychiatric adverse experiences have been reported in patients treated with efavirenz. In controlled trials of 1,008 patients treated with regimens containing efavirenz for an average of 1.6 years and 635 patients treated with control regimens for an average of 1.3 years, the frequency of specific serious psychiatric events among patients who received efavirenz or control regimens, respectively, were: severe depression (1.6%, 0.6%), suicidal ideation (0.6%, 0.3%), non-fatal suicide attempts (0.4%, 0%), aggressive behaviour (0.4%, 0.3%), paranoid reactions (0.4%, 0.3%), and manic reactions (0.1%, 0%). Patients with a history of psychiatric disorders appear to be at a greater risk of these serious psychiatric adverse experiences, with the frequency of each of the above events ranging from 0.3% for manic reactions to 2.0% for both severe depression and suicidal ideation. There have also been post-marketing reports of death by suicide, delusions and psychosis-like behaviour, although a causal relationship to the use of efavirenz cannot be determined from these reports.

Nervous System Symptoms

Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration, and abnormal dreaming are frequently reported side effects in patients receiving efavirenz 600 mg daily in clinical trials. In controlled clinical trials where 600 mg efavirenz was administered with other antiretroviral agents, 19.4% of patients experienced nervous system symptoms of moderate-to-severe intensity compared to 9% of patients receiving control regimens. These symptoms were severe in 2.0% of patients receiving efavirenz 600 mg daily and in 1.3% of patients...
receiving control regimens. In clinical trials 2.1% of patients treated with 600 mg of efavirenz discontinued therapy because of nervous system symptoms.

Nervous system symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2-4 weeks. In one clinical study, the monthly prevalence of nervous system symptoms of at least moderate severity between weeks 4 and 48, ranged from 5%-9% in patients treated with regimens containing efavirenz and 3%-5% in patients treated with the control regimen. In a study of uninfected volunteers, a representative nervous system symptom had a median time to onset of 1 hour post-dose and a median duration of 3 hours. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in patients who continue to experience these symptoms (see Dosage and Administration). Dose reduction or splitting the daily dose has not been shown to provide benefit and is not recommended.

**Laboratory Test Findings**

**Laboratory Abnormalities**

**Liver enzymes**

Elevations of AST and ALT to greater than five times the upper limit of the normal range were seen in 3% of 1,008 patients treated with 600 mg of efavirenz. Similar elevations were seen in patients treated with control regimens. In 156 patients treated with 600 mg of efavirenz who were seropositive for Hepatitis B and/or C, 7% developed AST levels and 8% developed ALT levels greater than five times the upper limit of the normal range. In 91 patients seropositive for Hepatitis B and/or C treated with control regimens, 5% developed AST elevations and 4% developed ALT elevations to these levels. Elevations of GGT to greater than five times the upper limit of the normal range were observed in 4% of all patients treated with 600 mg of efavirenz and in 10% of patients seropositive for Hepatitis B or C. In patients treated with control regimens, the incidence of GGT elevations to this level was 1.5-2%, regardless of Hepatitis B or C serology. Isolated elevations of GGT in patients receiving efavirenz may reflect enzyme induction not associated with liver toxicity (see Warnings and Precautions).

**Lipids**

Increases in total cholesterol of 10-20% have been observed in some uninfected volunteers receiving efavirenz. Increases from baseline in non-fasting total cholesterol and HDL of approximately 20% and 25%, respectively, were observed in patients treated with efavirenz+ZDV+3TC and of approximately 40% and 35%, in patients treated with efavirenz+IDV. The effects of efavirenz on triglycerides and LDL were not well-characterised. In another study, increases from baseline in total cholesterol, HDL-cholesterol, fasting LDL-cholesterol, and fasting triglycerides of 21%, 24%, 18%, and 23%, respectively, were observed in patients treated with efavirenz+ZDV+3TC for 48 weeks.

The clinical significance of these findings is unknown.
Interactions

Efavirenz is an inducer of CYP3A4. Other compounds that are substrates of CYP3A4 may have decreased plasma concentrations when co-administered with ARROW - EFAVIRENZ.

Concomitant Antiretroviral Agents

Fosamprenavir calcium

For guidance on co-administration with fosamprenavir and ritonavir, the prescribing information for fosamprenavir calcium should be consulted.

Atazanavir

Efavirenz decreases atazanavir exposure. Refer to the prescribing information for atazanavir guidance on co-administration with efavirenz.

Indinavir

When indinavir at an increased dose (1000 mg every 8 hours) was given with efavirenz (600 mg once daily) in uninfected volunteers, the indinavir AUC and Ctrough were decreased by approximately 33-46% and 39-57%, respectively compared to when indinavir was given alone at the standard dose (800 mg every 8 hours).

Similar differences in indinavir AUC and Cmax were also observed in HIV-infected subjects who received indinavir (1000 mg every 8 hours) with efavirenz (600 mg once daily) compared to indinavir given alone (800 mg every 8 hours). The optimal dose of indinavir, 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.

When efavirenz 600 mg once daily was given with indinavir/ritonavir 800/100 mg twice daily in HIV-1 infected patients (n=6), the pharmacokinetics of indinavir and efavirenz were generally comparable to these uninfected volunteer data.

Lopinavir/ritonavir

A significant reduction in the Cmin of lopinavir was observed when a lopinavir/ritonavir combination was coadministered with efavirenz compared to when the lopinavir/ritonavir combination was administered alone. A dose increase of lopinavir/ritonavir capsules or oral solution to 533/133 mg (4 capsules or 6.5 mL) twice daily taken with food should be considered when used in combination with efavirenz.

Consult the prescribing information for lopinavir/ritonavir tablets for guidance on coadministration of this formulation with efavirenz.

Maraviroc
The AUC12 and Cmax of maraviroc (100 mg twice daily) are decreased by 45% and 51%, respectively, when given with efavirenz (600 mg once daily) compared to maraviroc administered alone. Refer to the prescribing information for maraviroc for guidance on co-administration with efavirenz. (Maraviroc is not currently available in New Zealand.)

Ritonavir

When efavirenz 600 mg (given once daily at bedtime) and ritonavir 500 mg (given every 12 hours) was studied in uninfected volunteers the combination was not well tolerated and was associated with a higher frequency of adverse clinical experiences (e.g., dizziness, nausea, paraesthesia) and laboratory abnormalities (elevated liver enzymes).

Monitoring of liver enzymes is recommended when ARROW - EFAVIRENZ is used in combination with ritonavir.

Saquinavir

When saquinavir (1200 mg given 3 times a day, soft gel formulation) was given with efavirenz, the saquinavir AUC and Cmax were decreased by 62% and 45-50%, respectively. Use of efavirenz in combination with saquinavir as the sole protease inhibitor is not recommended.

HCV Protease Inhibitors

Boceprevir

When efavirenz (600 mg once daily) was given with boceprevir (800 mg three times daily) the plasma trough concentration of boceprevir was decreased. (Cmin ↓ 44%). The clinical outcome of this observed reduction has not been directly assessed.

Antimicrobial Agents

Rifamycins

Rifampin reduced efavirenz AUC by 26% and Cmax by 20% in 12 uninfected volunteers. The dose of ARROW - EFAVIRENZ should be increased to 800 mg/day when taken with rifampin. No dose adjustment of rifampin is recommended when given with ARROW - EFAVIRENZ. In one study in uninfected volunteers, efavirenz induced a reduction in rifabutin Cmax and AUC by 32% and 38% respectively and increased rifabutin clearance. Rifabutin had no significant effect on the pharmacokinetics of efavirenz. These data suggest that the daily dose of rifabutin should be increased by 50% when administered with ARROW - EFAVIRENZ and that the rifabutin dose may be doubled for regimens in which rifabutin is given two or three times a week in combination with ARROW - EFAVIRENZ.
Clarithromycin

Co-administration of 400 mg of efavirenz once daily with clarithromycin given as 500 mg every 12 hours for seven days resulted in a significant effect of ARROW - EFAVIRENZ on the pharmacokinetics of clarithromycin. The AUC and Cmax of clarithromycin decreased 39% and 26%, respectively, while the AUC and Cmax of the clarithromycin hydroxymetabolite were increased 34% and 49%, respectively, when used in combination with efavirenz. The clinical significance of these changes in clarithromycin plasma levels is not known. In uninfected volunteers 46% developed rash while receiving efavirenz and clarithromycin.

No dose adjustment of ARROW - EFAVIRENZ is recommended when given with clarithromycin. Alternatives to clarithromycin should be considered.

Antifungal Agents

Voriconazole

Co-administration of efavirenz (400 mg orally once daily) with voriconazole (200 mg orally every 12 hours) in uninfected volunteers resulted in a 2-way interaction.

The steady state AUC and Cmax of voriconazole decreased by 77% and 61%, respectively, while the steady state AUC and Cmax of efavirenz increased by 44% and 38%, respectively. Co-administration of standard doses of ARROW - EFAVIRENZ and voriconazole is contraindicated (see Contraindications).

Following co-administration of efavirenz (300 mg orally once daily) with voriconazole (300 mg twice daily) in uninfected volunteers, the AUC and Cmax of voriconazole was decreased by 55% and 36% respectively, compared to voriconazole 200 mg twice daily alone; AUC of efavirenz was equivalent but Cmax was decreased by 14% compared to efavirenz 600 mg once daily alone.

Following co-administration of efavirenz (300 mg orally once daily) with voriconazole (400 mg twice daily) in uninfected volunteers, the AUC of voriconazole was decreased by 7% and Cmax was increased by 23% compared to voriconazole 200 mg twice daily alone.

These differences were not considered to be clinically significant. The AUC of efavirenz was increased by 17% and Cmax was equivalent compared to efavirenz 600 mg once daily alone.

When efavirenz is co-administered with voriconazole, the voriconazole maintenance dose should be increased to 400 mg twice daily and the efavirenz dose should be reduced by 50%, i.e., to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.

Itraconazole

Co-administration of efavirenz (600 mg orally once daily) with itraconazole (200 mg orally every 12 hours) in uninfected volunteers decreased the steady state AUC, Cmax, and Cmin of itraconazole by 39%, 37%, and 44%, respectively, and of
hydroxyitraconazole by 37%, 35%, and 43%, respectively, compared to itraconazole administered alone. The pharmacokinetics of efavirenz were not affected. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.

**Posaconazole**

Co-administration of efavirenz (400 mg orally once daily) with posaconazole (400 mg orally twice daily) decreased the AUC and Cmax of posaconazole by 50% and 45%, respectively, compared to posaconazole administered alone. Concomitant use of posaconazole and ARROW - EFAVIRENZ should be avoided unless the benefit to the patient outweighs the risk.

**Antimalarial agents**

**Atovaquone and proguanil hydrochloride**

Coadministration of efavirenz (600 mg once daily) with atovaquone and proguanil (250/100 mg single dose) reduces the AUC and Cmax 75% and 44% for atovaquone and the AUC 43% for proguanil via the induction of glucuronidation. Concomitant administration of atovaquone/proguanil with efavirenz should be avoided whenever possible.

**Lipid Lowering Agents**

Co-administration of efavirenz with the HMG-CoA reductase inhibitors atorvastatin, pravastatin, or simvastatin has been shown to reduce the plasma concentration of the statin in uninfected volunteers. Cholesterol levels should be periodically monitored. Dosage adjustments of statins may be required.

**Atorvastatin**

Co-administration of efavirenz (600 mg orally once daily) with atorvastatin (10 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and Cmax of atorvastatin by 43% and 12%, respectively, of 2-hydroxy atorvastatin by 35% and 13%, respectively, of 4-hydroxy atorvastatin by 4% and 47%, respectively, and of total active HMG-CoA reductase inhibitors by 34% and 20%, respectively, compared to atorvastatin administered alone.

**Pravastatin**

Co-administration of efavirenz (600 mg orally once daily) with pravastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and Cmax of pravastatin by 40% and 18%, respectively, compared to pravastatin administered alone.

**Simvastatin**

Co-administration of efavirenz (600 mg orally once daily) with simvastatin (40 mg orally once daily) in uninfected volunteers decreased the steady-state AUC and Cmax of simvastatin by 69% and 76%, respectively, of simvastatin acid by 58% and
51%, respectively, of total active HMG-CoA reductase inhibitors by 60% and 62%, respectively, and of total HMG-CoA reductase inhibitors by 60% and 70%, respectively, compared to simvastatin administered alone.

Co-administration of efavirenz with atorvastatin, pravastatin, or simvastatin did not affect efavirenz AUC or Cmax values. No dosage adjustment is necessary for ARROW - EFAVIRENZ.

**Anticoagulants**

**Warfarin/Acenocoumarol**

Plasma concentrations and effects potentially increased or decreased by efavirenz.

**Anticonvulsants**

**Carbamazepine**

Co-administration of efavirenz (600 mg orally once daily) with carbamazepine (400 mg once daily) in uninfected volunteers resulted in a two-way interaction. The steady-state AUC, Cmax and Cmin of carbamazepine decreased by 27%, 20% and 35%, respectively, while the steady-state AUC, Cmax and Cmin of efavirenz decreased by 36%, 21%, and 47%, respectively. The steady-state AUC, Cmax and Cmin of the active carbamazepine epoxide metabolite remained unchanged. Carbamazepine plasma levels should be monitored periodically. There are no data with co-administration of higher doses of either medicinal product; therefore, no dose recommendation can be made, and alternative anticonvulsant treatment should be considered.

**Other anticonvulsants**

No data are available on the potential interactions of efavirenz with phenytoin, phenobarbital, or other anticonvulsants that are substrates of CYP450 isozymes. When ARROW - EFAVIRENZ is administered concomitantly with these agents, there is a potential for reduction or increase in the plasma concentrations of each agent; therefore, periodic monitoring of plasma levels should be conducted. Specific interaction studies have not been performed with efavirenz and vigabatrin or gabapentin. Clinically significant interactions would not be expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine and would be unlikely to compete for the same metabolic enzymes and elimination pathways as efavirenz.

**Other Medicine Interactions**

**Hormonal Contraceptives**

Oral: When an oral contraceptive (ethinyl estradiol 0.035 mg/norgestimate 0.25 mg once daily) and efavirenz (600 mg once daily) were co-administered for 14 days, efavirenz had no effect on ethinyl estradiol concentrations but plasma concentrations of norelgestromin and levonorgestrel, active metabolites of norgestimate, were
markedly decreased in the presence of efavirenz (64%, 46%, and 82% decrease in norelgestromin AUC, Cmax and Cmin, respectively, and 83%, 80%, and 86% decrease in levonorgestrel AUC, Cmax, and Cmin, respectively). The clinical significance of these effects is not known. No effect of ethinyl estradiol / norgestimate on efavirenz plasma concentrations was observed.

Injection: Limited information exists regarding efavirenz and injectable hormonal contraception. In a 3 month medicine interaction study of depo-edroxyprogesterone acetate (DMPA) and efavirenz, plasma progesterone levels for all subjects remained below 5 ng/mL, consistent with suppression of ovulation.

Implant: The interaction between etonogestrel and efavirenz has not been studied. Decreased exposure of etonogestrel may be expected (CYP3A4 induction), and there have been occasional post-marketing reports of contraceptive failure with etonogestrel in efavirenz-exposed patients.

**Immunosuppressants**

When an immunosuppressant metabolized by CYP3A4 (eg, cyclosporine, tacrolimus, or sirolimus) is administered with efavirenz, decreased exposure of the immunosuppressant may be expected due to CYP3A4 induction. Dose adjustments of the immunosuppressant may be required. Close monitoring of immunosuppressant concentrations for at least 2 weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with efavirenz.

**Methadone**

In a study of HIV-infected IV drug users, co-administration of efavirenz with methadone resulted in decreased plasma levels of methadone and signs of opiate withdrawal. The methadone dose was increased by a mean of 22% to alleviate withdrawal symptoms. Patients should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

St. John’s wort (Hypericum perforatum): Patients on ARROW - EFAVIRENZ should not concomitantly use products containing St. John’s wort (Hypericum perforatum) since it may be expected to result in reduced plasma concentrations of ARROW - EFAVIRENZ. This effect is due to an induction of CYP3A4 and may result in loss of therapeutic effect and development of resistance.

**Anti-depressants**

There were no clinically significant effects on pharmacokinetic parameters when paroxetine and efavirenz were co-administered. No dose adjustments are necessary for either ARROW - EFAVIRENZ or paroxetine when these medicines are co-administered.

Sertraline did not significantly alter the pharmacokinetics of efavirenz. Efavirenz decreased sertraline Cmax, C24, and AUC by 28.6 - 46.3%. The dose of sertraline should be increased when administered with ARROW - EFAVIRENZ to compensate for the induction of sertraline metabolism by ARROW - EFAVIRENZ. Sertraline dose increases should be guided by clinical response.
Bupropion (150 mg single dose, sustained release) when given with efavirenz (600 mg once daily) reduced the AUC and Cmax by 55% and 34% respectively. The AUC of hydroxybupropion was unchanged and the Cmax was increased via CYP2B6 induction by 50%. Increases in bupropion dose should be guided by clinical response, but should not exceed the maximum recommended dose. No adjustment of efavirenz is required.

Cetirizine

Cetirizine had no clinically significant effect on efavirenz pharmacokinetic parameters. Efavirenz decreased cetirizine Cmax by 24% but did not alter cetirizine AUC.

These changes are not expected to be clinically significant. No dose adjustments are necessary for either ARROW - EFAVIRENZ or cetirizine when these medicines are co-administered.

Lorazepam

Efavirenz increased lorazepam Cmax and AUC by 16.3% and 7.3%, respectively. The pharmacokinetic interaction of ARROW - EFAVIRENZ on lorazepam is unlikely to be clinically significant. No dose adjustments are necessary for either ARROW - EFAVIRENZ or lorazepam when these medicines are co-administered.

Calcium channel blockers

Co-administration of efavirenz (600 mg orally once daily) with diltiazem (240 mg orally once daily) in uninfected volunteers decreased the steady state AUC, Cmax, and Cmin of diltiazem by 69%, 60%, and 63%, respectively; desacetyl diltiazem by 75%, 64%, and 62%, respectively; and N-monomodesmethyl diltiazem by 37%, 28%, and 37%, respectively, compared to diltiazem administered alone. Diltiazem dose adjustments should be guided by clinical response (refer to the data sheet for diltiazem).

Although the pharmacokinetic parameters of efavirenz were slightly increased (11% - 16%), these changes are not considered clinically significant and, thus, no dosage adjustment is necessary for efavirenz when administered with diltiazem.

No data are available on the potential interactions of efavirenz with other calcium channel blockers that are substrates of the CYP3A4 enzyme (eg, verapamil, felodipine, nifedipine, nicardipine). When efavirenz is administered concomitantly with one of these agents, there is a potential for reduction in the plasma concentrations of the calcium channel blocker. Dose adjustments should be guided by clinical response (refer to the corresponding manufacturer's data sheet for the calcium channel blocker).

Cannabinoid Test Interaction
ARROW - EFAVIRENZ does not bind to cannabinoid receptors. False positive urine cannabinoid test results have been reported in uninfected volunteers who received efavirenz.

False positive test results have only been observed with the CEDIA DAU Multi-Level THC assay, which is used for screening, and have not been observed with other cannabinoid assays tested including tests used for confirmation of positive results.

**Overdosage**

Some patients accidentally taking efavirenz 600 mg twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Treatment of overdose with ARROW - EFAVIRENZ should consist of general supportive measures, including monitoring of vital signs and observation of the patient’s clinical status.

Administration of activated charcoal may be used to aid removal of unabsorbed medicine.

There is no specific antidote for overdose with ARROW - EFAVIRENZ. Since ARROW - EFAVIRENZ is highly protein bound, dialysis is unlikely to significantly remove the medicine from blood.

**Pharmaceutical Precautions**

**Storage**

Store below 25°C.

**Shelf Life**

3 years

**List of excipients**

Microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, sodium lauryl sulphate, lactose monohydrate and magnesium stearate. The film coat contains Opadry Yellow 15B 82855 and purified water.

**Medicine Classification**

Prescription Medicine

**Package Quantities**

Bottles: 30 and 60 tablets

Blister packs: 30 and 90 tablets
Further Information

Nil.

Name and address

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