EDITORIAL

The indispensable role played by drugs in the improvement of health situation of any given society is a well-known fact. Information targeting rational use of every drug is a guarantee towards ensuring availability of safe, effective and quality drugs.

In this first issue, the National resource center, DACA, has given more emphasis to the drugs now emerging in the international market to alleviate the current national and international problem, which is HIV/AIDS. Though *antiretroviral drugs* are not curative, they have proven to be effective in improving the quality and prolonging the life of the victims. Of the twelve antiretroviral drugs included in the National List of Drugs for Ethiopia, Six discussed in this issue and the rest will be covered in the coming issues. However, other issues considered to be pertinent and current are addressed as well, in four columns of the bulletin, which will assume to be regular. All the four topics are prepared by the staffs of the authority. But for the future we expect much from all readers in general and professionals in particular, above all health is a fundamental human right.

In the coming issues there will be a fifth column "readers view" where everyone is most welcome to foreword his suggestion. Hence you are kindly invited to contribute any relevant information in line with the aim & content of the bulletin and we have a strong believe that your active participation will help us to materialize our target.

Message from the General Manager

These days Information is not only power but it is a vital ingredient of every day's life of every one of us. However every information piece may not be always beneficial, crucial, accurate, dependable & generic and the scope of the message every information carries may target a definite subject or a group.

In such situation where it is difficult to determine the above quality of information standardization and regulation is essential. Otherwise the risk of endangering the health and life of consumers will be extremely high and unacceptable.
To this end efforts have been underway at international & National level. Guidelines on the identification, retrieval, development, and communication of information related to Drugs issued by pertinent bodies like WHO are serving as invaluable references.

In fact a medical product will simply be considered as "a chemical only" if not accompanied by appropriate information were the quality of the information is equally important as the quality of the active substance.

At a National Level DACA is designated to serve as a National Drug Information resource Center as well as a regulator by the Federal Government. Since its establishment one year ago, the Authority has put Drug Information dissemination as one of the prime tasks in its agenda. Among the efforts done so far, after its discontinuation for some years, now we are able to forward to you the first issue of the Drug Information Bulletin (DIB).

We believe that this bulletin will alleviate the scarcity of information on Health & Pharmaceutical issues, which are challenging the professional at all level and area of assignment & specially those in the periphery. Utmost efforts will be done to avail copies of the bulletin to most pharmacy professionals and those at place with scarce opportunity to Drug Information.

The Authority is determined to establish and ensure reputation of the bulletin at National and International level. But the determination is built on the concept of a partnership, which calls for contribution and involvement of all potential actors - dispenser, consumer, prescriber, regulator, producers and other users of the bulletin.

Hence a common ground that will prove our ambition in forging partnership is our commitment, therefore lets play our role to produce a well-informed and responsible professional at all times.
Thank you
Haile selassie Bihon
General Manager, Drug Administration and control Authority of Ethiopia

Background

HIV/AIDS has been known since two decades; today globally around 40 million people are living with the virus, of which 95 % are in developing countries, especially in Sub-Saharan Africa. HIV/AIDS is among the leading cause of death in the world, Some 3 million people died in 2000 (over 15,000 new HIV infections per daily).

By the end of 1999 the number of people living with HIV/AIDS (PLHA) in Ethiopia was 3 million (South Africa 4. 2 million). In 2000, USAID released a study concluded that over 34million children had lost one or both parents due to AIDS or other causes. In five Sub-Saharan African countries, more than 20% of children younger than 15 are orphans. In other countries, more than 15% of children fall in to this category. In addition, there are nearly 3million children infected with the virus. Last year, over 800,000 children contracted HIV/AIDS, primarily through mother- to- child transmission of HIV, and the overwhelming majority of these cases is in Sub-Saharan Africa. Most of the 580,000 children under the age of 15 who died of HIV/AIDS in 2001 were African. Its impact will become even more severe. No vaccine, no curative measures available, mainly paralyzing people of productive age group and it is spreading fast in an alarming speed.

The virus.

Viruses are obligate intracellular parasites, which are very small (20nm and 250 nm in diameter) containing predominantly only one kind of nucleic Acid (DNA or RNA), which is surrounded by at least one layer of protein. Viruses have shown that infection is a genetic phenomenon due to release of viral genetic material, which may be DNA or RNA, into the cell.
This genetic material then uses the synthetic machinery of the cell to replicate its nucleic acid and to make new viral capsid components, which are later assembled into new, mature virus particles.

HIV is a retrovirus discovered by Barre-Sinoussie, montagnier, and colleagues at the institute of Pasteur, Paris, in 1983 and given the name lymphadeneopathy associated virus (LAV). In 1984 Popovic, Gallo and coworkers described the development of cell lines permanently and productively infected with virus and, in line with two previously described retroviruses HTLV-I and HTLV-II, they designated the virus HTLV-III, LAV.
Retroviruses carry their genetic information in RNA rather than DNA,
Host Machinery
DNA $\Rightarrow$ RNA $\Rightarrow$ Protein
The HIV uses reverse machinery
RNA $\Rightarrow$ DNA $\Rightarrow$ RNA $\Rightarrow$ Protein

There are two major types of HIV, these are HIV1 and HIV2.Again HIV1 has six major subtypes A – F, and outliers, HIV – 10. HIV –2 is uncommon out side west Africa. Like some other RNA viruses, HIV is very liable, and consequent shifts in host range and virulence would explain how new pathogenic retroviruses could arise in man. Retroviruses are so named because their genomes encode an unusual enzyme, reverse transcriptase, which allows DNA to be transcribed from RNA. Thus HIV can make copies of its own genome, as DNA, in host cells such as the human CD4 "Helper" lymphocyte. The viral DNA becomes integrated in the lymphocyte genome, and this is the basis for chronic HIV infection. This integration of the HIV genome into the host cells is likely to be a formidable obstacle to the development of any antiviral agent that would not just suppress but also eradicate the infection. The inherent variability of the HIV genome and the failure of the human host to produce neutralizing antibodies to the virus, as well as technical difficulties and concerns about safety, continue to frustrate attempts to make an effecti vaccine.

Anti Retroviral Therapy (ART)

Antiretroviral drugs are drugs, which are effective against HIV. Knowledge about the clinical efficacy and basic pharmacology of these drugs is paramount important in the initiation of

therapy and patient counseling. This includes knowledge on their adverse drug reaction, prediction of emergence of drug resistance, drug interaction (as such patients are frequently taking multiple medications for treatment or prophylaxis of opportunistic infections and for relieving pain), etc. To avoid the emergence of drug resistance ART is given in combination.

The aim of ART is maximal suppression of HIV replication with minimum adverse effect accompanied by good patient compliance with the adherence to the prescribed regiment for specific drug combination.

Aim

- To decrease level of viral load in HIV infected patients.
- To intercept viral transmission in pregnancy
- For post exposure prophylaxis for health care workers
- For post exposure prophylaxis for sexual contact or needle sharing.

Classifications

ARVs are classified into three groups

1. Reverse Transcriptase inhibitors

A – Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Zidovudine (Azidothymidine – ZDV or AZT)
- Didanosine (Dideoxyinosine, DDI)
- Lamivudine (3TC)
- Zalcitabine (Dideoxycystocine, DDC)
- Stavudine (d4T)
- Abacavir (ABC)

B – Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Nevirapine(NVP)
- Delaviridine(DLV)
- Efavirenz(EFV)

2. Protease Inhibitors (PIs)

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (FV)
- Amprenavir (APV)

1.A. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

These are synthetic dideoxynucleosides

Mechanism of action:

These drugs are phosphorylated by intracellular kinase to the corresponding triphosphates. These triphosphates compete with equivalent cellular triphosphates, which are essential substrates for the formation of pro-viral DNA synthesis resulting in inhibition of viral replication by chain termination.

Properties: -

- They were the first available agents in the treatment of HIV infection.
- Most have activities against both HIV_1, and HIV_2
- There is low to moderate cross resistance among the drugs
- Cause fatty changes in the liver or lactic acidosis due to toxicity on cellular mitochondria.
- Long-term use brings about derangement in fat metabolism.

1.B Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Mechanism of action: -

Bind directly to a site on the viral reverse transcriptase that is near but distinct from the binding site of NRTIs without getting phosphorylated and without competing with nucleoside triphosphates, resulting in blockade of RNA-and DNA-dependent DNA polymerase activities.

Properties: -

- They have specific actions against HIV-1.
- They cause mild rash and elevation of serum aminotransferases
- Emergence of resistance due to K103N mutation as well as Y181 C/1 mutation.

- Monotherapy is not recommended because of rapid development of resistance.
- Cross-resistance among the drug is high.
- No cross-resistance between NNRTIs and NRTIs.

2. Protease Inhibitors (PIs)

Mechanism of action: -

These drugs inhibit protease, which is responsible for cleaving the immature
Precursor molecules in order to produce final structural proteins of the mature virion core. This results in inhibition of production of mature infectious virions during HIV replication so that new waves of infection will be prevented.

Properties: -

- Resistance emergence is rapid, due to specific genotype alteration, therefore combination with other groups ARV drugs is necessary.
- Cross-resistance among this group is moderate to high.
- The major adverse effects of this class of drugs are associated with alteration in fat distribution in the body. Such symptoms include buffalo hump, truncal obesity with facial and peripheral atrophy, insulin resistance and hyperlipidemia. They also bring about spontaneous bleeding in patients with hemophilia A or B.
- Active against HIV_1 only
- All undergo oxidative metabolism by cytochrome P450 enzyme

Zidovudine(Azidothymidine,AZT,Retrovir)

Pharmacokinetics

Mechanism of action – see for the NRTIs

Absorption.
Rapid and nearly complete absorption from the GIT following oral administration; however, because of first – pass metabolism systemic bioavailability of zidovudine capsules and solution is approximately 65 % (range, 52 to 75 %). Bioavailability in neonates up to 14 days of age is approximately 89 %, and in neonates over 14 days of age it decreases to approximately 61 %. Administration with a high-fat meal may decrease the rate and extent of absorption.

Distribution

- Crosses the Blood-Brain barrier; distribution to the CSF averages approximately 24 % of the plasma concentration in children.
- Cross the placenta
- Also shown to concentrate in the semen of HIV – infected patients with concentrations ranging from 1.3 to 20.4 times those found in the serum; zidovudine does not appear to affect the recovery of HIV from the semen, and therefore, may not prevent sexual transmission of HIV.
- Low protein binding (30 to 38 %)
- Metabolized by the liver
  Half – life
  Intracellular Zidovudine – triphosphate – 3.3 hrs.

Zidovudine (serum) – Adults (oral and i.v.) = 1 hr. for normal renal function but increase when there is renal impairment.

Time to peak concentration: -
Serum – 0.5 to 1.5 hrs.
CSF – 1 hour after end of 1 hour infusion
Elimination – Renal (in urine)

Precaution

Breast-feeding:

Zidovudine is distributed into human breast milk. HIV – infected mothers are not advised breast-feeding so as to avoid post-natal

transmission of HIV.
Pediatrics:
It can be used in children 3 months of age and older. The pharmacokinetics of zidovudine in children 14 days of age and older have been found to be similar to those in adults. The half-life in newborns was found to be 10 times that of the mother (13 vs 1.3 hrs, respectively). The side effects seen in children, including hematologic effects, were also similar to those seen in adults.

Drug Interactions:

Bone barrow depressants, clarithromycin, Ganciclovir, Interferon-alfa, Probenecid, Ribavirin, Atovaquone, Phenytoin, Fluconazole.
Mean corpuscular Volume (MCV) will usually be increased in patients taking zidovudine. Complete blood counts (CBCs) and Liver function test should be carried out. It is recommended that blood tests should be carried out every 2 weeks for the first three months of treatment, and at least monthly thereafter in patients taking oral Zidovudine and at least every week in those receiving intravenous Zidovudine.

Side/Adverse Effects

It is often difficult to differentiate between the manifestations of HIV infection and the adverse effects of Zidovudine.

Incidence more frequent
Anaemia, Leukopenia or neutropenia (especially for patients in advanced HIV infection), severe headache, insomnia, myalgia, nausea.
Incidence less frequent
Changes in platelet count (often increased with therapy; however, may be decreased infrequently), changes in skin pigmentation hyperpigmentation of nails.

Incidence rare – Hepatotoxicity, lactic acidosis, Myopathy, neurotoxicity, bone marrow depression.

Patient consultation

- Consider points like pregnancy, breast feeding, dental (Bone marrow depression by zidovudine may result in an increased incidence of certain microbial infections and delayed healing), other medications like alfainterferon, bone marrow depressants clarithromycin, gancic-lovir, probencid, or ribavirin, medical problems (especially bone marrow depressions or hepatic function impairment).
- Importance of not taking the medication above the prescribed, discontinuing without checking with physicians, compliance full to course of therapy.
- Importance of not missing doses and taking at evenly spaced times, In case of missed dose – taking as soon as possible or not taking if almost time for the next dose; not doubling doses

- Proper storage

Precautions while using this medication

- Regular visits to Physician for blood tests

- Importance of not taking other medications concurrently without checking with the physician. Using caution in use of regular toothbrushes, dental floss, and tooth picks, checking with physician or dentist concerning proper oral hygiene.

- Avoiding sexual intercourse or using condom to help prevent transmission of the AIDS virus to others; not sharing needles with anyone.

Dose

Zidovudine infusion should be administered at a constant rate over a period of 1 hr. It should not be administered intramuscularly or by rapid infusion or direct injection.

Patients with significant anemia (Hgb 7.5 gm/dL) and/or significant granulocytopenia (granulocyte count of 750 cell/mm3) may require interruption of zidovidine therapy until bone marrow recovery is seen. In patients with less severe anemia or granulocytopeneia, a reduction in the daily dose may be adequate. However, in patients with significant anemia, dose modification may not eliminate the need for

transfusion. If bone marrow recovery occurs following dose modification, gradual increase in dose may be appropriate, depending on hematologic indices and patient tolerance.
Granulocytopenia and anemia have been shown to be inversely related to the CD4 lymphocyte count, hemoglobin concentration, and granulocyte count, at time of therapy initiation, and directly related to dosage and duration of therapy. Significant anemia most commonly occurs after 4 to 6 weeks of therapy.

Patients with anemia usually improve when zidovudine is discontinued or the dose reduced. However, even with lower doses, patients may require blood transfusions or, in selected patients, treatment with epoetin (recombinant human erythropoietin). Patients with granulocytopenia may require interruption of therapy or treatment with Granulocyte macrophage colony stimulating Factor (GM – CSF).
If a patient receiving zidovudine develops unexplained dyspnea, tachypnoea, or a fall in serum bicarbonate concentration, therapy with zidovuidine should be suspended until the diagnosis of lactic acidosis can be ruled out. Treatment with zidovudne also should be suspended in the case of rapid elevations of serum aminotransferase concentrations or progressive hepatomegaly of unknown etiology.

Oral dosage forms, Zidovudine capsules

Usual adult and adolescent dose:
Monotherapy
Symptomatic or asymptomatic HIV infection
Oral, 100 mg every four hours while awake (500 mg/day) or 600 mg/day in divided doses.

Note: Patients with end-stage renal disease require a reduction in dose to 100mg orally every 6 to 8 hours.
Combination therapy with other antiretroviral agents: -
Oral, 600 mg/day in divided doses (300 mg every 12 hrs or 200 mg every 8 hrs).

Combination therapy with zalcitabine

Oral, 200 mg of zidovudine and 75 mg of zalcitabine given together every eight hours.

Maternal – fetal HIV transmission (Prophylaxis) -
Oral, 100 mg 5x/day beginning after 14 weeks of gestation and continuing until the start of labor. At that time zidovudine Iv should be administered (2 mg/kg body weight infused over 1 hr, followed by a continuous infusion of 1 mg/Kg body wt/hr until clapping of the umbilical cord).

Usual pediatric dose:
Symptomatic or a symptomatic HIV infection
Infants up to 3 months of age Dosage has not been established; children 3 months to 12 years of age oral 90 to 180 mg per square meter of body surface every six hours.

Children 12 years of age and older usual adult dose
Note – Dosage should not exceed 200 mg every six hour.
Pediatric patients with granulocytopenia may require a dose reduction to 120 mg per square meter of body surface every six hours.

Parenteral zidovudine

Usual adult dose – 1 mg/Kg body weight, infused over 1 hr, every four hours, 5 to 6 times a day (5 to 6 mg/Kg/day) until oral therapy can be administered.
Note: -1 mg/Kg body weight. every 4 hrs is equivalent to oral administration of 100 mg every four hours.

Preparation of dosage form:

Zidovudine injection just be diluted prior to administration to concentration of no greater than 4 mg/ml in 5 % dextrose inj., 0.9 % NaCl inj. 5 % dextrose and 0.45 % NaCl inj., Lactated Ringer's inj, or 5 % dextrose and Lactated Ringer's injection.

Stability: -

After dilution, solutions are physically and chemically stable for 24 hrs at room temperature (25°C or 77 °F) and 48 hrs if refrigerated (2 to 8 °C, or 36 to 46 °F) to minimize potential microbial contamination.

The solution should be visually inspected prior to administration for discoloration and particulate matter. If either of these is detected, the solution should be discarded.

Incompatibilities

Zidovudine injection should not be admixed with biological or colloidal solutions (e.g. Blood products, protein containing solutions).

Packaging and storage

Store between 15 and 25 °c (59 and 77 °F), in a tight container. Protect from light and Moisture.

LAMIVUDINE (3TC)

Lamivudine is the negative enantiomer of 2"-deoxy – 3" - thiacytidine (negative enantiomer was found more active and less toxic).

Lamivudine has invitro activity against HIV - 1 and HIV - 2, including zidovudine resistant isolates, as well as Hepatitis B virus. It is indicated that in combination with other antiretroviral agents for the treatment of HIV infection, especially with Zidovudine its combination has been found to be synergistic effect (in invitro).

Pharmacokinetics

Mechanism of action – see for the NRTIs group

Absorption
Readily absorbed; bioavailability in adults and adolescents in 80 to 88 % and in children is approximately 66 to 68 %. Food delays the peak serum concentration and the time to peak serum concentration; however, there is significant difference in bioavailability. Therefore lamivudine may be administered with food or without food.

Distribution
Widely distributed; crosses the blood brain barrier, CSF and the placenta. Has low protein binding.

Half life - Intracellular L - TP 11 to 15 hrs
- Lamivudine (serum) - Adults 2 to 11 hrs
- Children (4 months to 4 yrs)- 1.7 to 2 hrs

Renal function impairment
- Creatinine clearance 10 to 40 ml/min (0.17 to 0.67 ml/sec)
  = approximately 13.6 hrs

- Creatinine clearance less than 10 ml/min (0.17 ml/sec)
  = Approximately 19.4 hrs.

Time to peak concentration
- Approximately 0.5 to 2 hrs after a single 100 mg dose

With food - Approximately 3.2 hrs
Fasting - Approximately - 1 hour

Peak serum concentration
Adults and adolescents - 2-mg/Kg body wt.: 1.5 mcg/ml (6.5 micromoles/liter)

Children - 8 mg/Kg: 1.1mcg/ml (4.8 micromoles/liter)

Elimination
Renal: the majority (68 - 71 %) of lamivudine is eliminated unchanged in the urine; approximately 5.2 % of the trans-sulfoxide metabolite is excreted in the urine with in 12 hrs. The renal clearance of lamuvidine is greater than the glomerular filtration rate; implying active secretion into the renal tubules.

Drug intractions and related problems

Drugs associated with pancreatitis (such as alcohol, didanosine, intravenous pentamidine, sulfonamides, or zalicitabine), & drugs associated with peripheral neuropathy, such as

didanosine, dapsone, Isoniazide, stavudine, or zalcitabine should be avoided or, if concurrent use is necessary, use with caution,

Indinavir - may decrease AUC of lamivudine
Sulfamethoxazole and trimethoprim - increase AUC and decrease in renal clearance of lamivudine.

Laboratory value alterations:
Alanine aminotrasferase (ALT/SGPT) and
Aspartate aminotransferase (AST/SGOT) (an increase in serum transaminses may be observed)
Amylase, serum (values may be increased)
Haemoglobin concentrations and Neutrophil count values may be increased.

Medical considerations:

Lamivudine tablets and oral solution can be used for the treatment of Heaptitis B, in such case it is given in lower dose than for the treatment of HIV. If lamivudine treatment for Hepatitis B is prescribed for a patient with unrecognized or untreated HIV, rapid emergence of HIV resistance to lamivudine is likely to occur because of sub therapeutic dose and inappropriate monotherapy.

- Hyper sensitivity to lamivudine
- pancreatitis, or history of
- Peripheral neuropathy or history of
- Renal function impairment

Creatinine Clearance (ml/min/mlsec)	**Dose**
≥50/0.83	150mg twice a day
30-49/0.50-0.82	150mg once a day
15-29/0.25 - 0.48	150mg first dose, then 100mg once a day
5-14/0.08 - 0.23	150mg first dose, then 50mg once a day
< 5/<0.08	50mg first dose, then 25mg once a day

Patient monitoring – SGPT,SGOT, amylase (serum), Lipase (serum),
Triglycerides (serum) blood urea Nitrogen (BUN) & creatinine (serum).

Side/Adverse effects: -

Incidence more frequent
Pancreatitis - its signs include nausea, vomiting, sever abdominal or stomach pain
Paresthesias and peripheral neuropathy - sign →tingling, burning numbness, or pain in the hands, arms, feet, or legs
Incidence less frequent –
Anemia (usual signs tiredness), severe hepatomegaly with steatosis (sign-abdominal discomfort; feeling fullness), lactic acidosis (abdominal discomfort; decreased appetite, muscle pain or cramping; nausea; shortness of breath; sleepiness; usual firedness or weakness); Neutropenia (fever, chills or sore throat); skin Rash. Cough, dizziness; fatigue, GI distress, headache, insomnia. Rarely, Hair loss.

General Dosing information

Lamivudine may be taken on a full or empty stomach. Before beginning treatment of HepatitisB infection, patients should be assessed by a physician experienced in the management of chronic hepatitis B.
Hepatitis B Virus -Adults and adolescents with renal function impairment require a reduction in dose as follows:

Creatinine Clearance (ml/min/ml/sec)	**Dose**
≥50/0.83	100mg twice a day
30-49/0.50-0.82	100mg first dose, then 50mg once a day
15-29/0.25-0.48	100mg first dose, then 25mg once a day
5-14/0.08 - 0.23	35mg first dose, then 15mt once a day
< 5/<0.08	35mg first dose, then 10mg once a day

HIV-Adults& adolescents with renal function im- pairment require a reduction in dose as follows.

ORAL SOLUTION

Usual adult and adolescent dose: -
Chronic hepatitis B- treatment, oral -100 mg once a day.

The optimum duration of treatment is unknown.
HIV/AIDS - treatment- weight for ≥ 50 Kg, oral, 150 mg of lamivudine twice a day in combination with zidovudine.
200 mg three times a day or with other antiretroviral agents.
Adults weighing <50 kg, oral, 2 mg per Kg of body weight of lamivudine twice a day in combination with zidovudine 200 mg three times a day or with other antiretroviral agents.
Prophylaxis - oral, 150 mg lamivudine twice a day, in combination with zidovudine 200 mg three times a day, for four weeks. A protease inhibitor may also be added to the regimen.

Usual Pediatric dose

- Chronic Hepatitis B treatment for children above 16 years of age - see adult dose.
- Children <16 years of age safety and efficacy have not been established.

HIV/AIDS treatment

- Children ≥16 years = Adult dose
- Children 3 months to 16 years of age, oral - 4 mg/Kg body weight of lamivudine, up to a 150 mg dose, twice a day in combination with 180 mg per square meter of body surface of zidovudine every six hours or with other antiretroviral agents.
- Children up to 3 months of age: safety and efficacy have not been established, Reduce dose in children with renal impairment.

Packaging and storage
Store between 2 and 25^{o}c (36 and 77^{o}F) in a tight container. For tablet 2 and 30^{o}c (36 and 86 F).

Auxiliary labeling.

Continue medicine for full time of treatment.

Note- When dispensing, include a calibrated liquid measuring device.

DIDANOSINE (DDI)

Didanosine is nucleoside analog reverse transcrptase inhibitor indicated in the treatment of adults and children over 6 months of age with advanced HIV infection who are intolerant of zidovudine therapy or who have demonstrated significant clinical or immunologic deterioration during zidovudine therapy. Didanosine is also used in combination with zidovudine.

Pharmacokinetic

Mechanism of action – see for the NRTIs group.

Absorption
Didanosine is acid labile; all oral formulations contain or are compounded with buffering agent to increase the gastric P^{H}; this results a decreased breakdown of didanosine and a subsequent increase in absorption. All formulations should be taken in an empty stomach. Administration within 5 minutes of a meal decreases the peak plasma concentration (C_{max}) and mean area under the plasma concentration versus time curve (AUC) by approximately 50 %. If didanosine is not buffered in the stomach, it forms 2,3 - dideoxy ribose and hypoxanthene, a precursor of uric acid.

Bioavailability - extremely variable in both adults and children.
Adults - approximately 33 to 37 %
Children (7 months to 19 years) - Average 19 to 42% (Range, 2 to 89%)

Distribution

- crosses blood - brain barrier and distributes into the CSF.
- Low protein binding (<5%)

Biotransformation : -

Rapidly metabolized intracellular to its active moiety, ddA - Tp.
Half-life:
Adults - Approximately 1.5 hours (range, 0.8 to 2.7 hours)
Children - Approximately 0.8 hour (range, 05-12 hours)
Severe renal failure - Approximately 4.5 hours.
Intracellular half - life of ddA - TP is 8 to 24 hours, in vitro.

Time to peak concentration - 0.5 to 1 hour
Peak serum concentration

Adults -

Approximately 1.6 mcg/ml after a single 375-mg dose of buffered powder for oral solution, or 300 mg, dose of buffered chewable/dispersible tablet.

Children (8 months to 18 years of age) Steady state values after oral administration of 80, 120 and 180 mg per square meter of body surface were 0.8, 1.4 and 1.7 mcg/ml respectively.

Elimination: -
Renal clearance by glomerular filtration and active tubular secretion makes up approximately 50 % of the total body clearance.

Precautions to consider
Pregnancy - Didanosine crosses the placenta. However, studies in humans have not been done. Unlike zidovudine, it is not known whether didanosine reduces perinatal transmission of HIV infection.

Drug interactions and/or Related problems.

- ♠ Alcohol, Asparaginase, Azathioprine, Estrogens, Furosemide, sulfonamides, sulindac, tetracycline, Thiazide diuretics, valporic acid and other drugs associated with pancreatitis should be avoided or used cautiously during didanosine therapy.

- ♠ Drugs associated with peripheral neuropathy: - Chloramphenicol, cisplatin, Dapsone, Ethambutol, Ethionamide, Hydralazine, Isoniazid, Lithium, Metronidazole, Nitrofurantoin, Nitrous oxide, phenytoin, stavudine, vincristine, Zalcitabine or other drugs inducing perpheral neuropathy should be avoided during didanosin therapy or, if concurrent use is necessary, use with caution.

- ♠ Dapsone and any other medications that also depend on gastric acidity for optimal absorption, such as itraconazole and ketoconazole, should be administered at least 2 hours before or 2 hours after didanosine is given.

Similarly, Fluoroquinolone antibiotics such as ciprofloxacin, enoxacin, Lomefloxacin, norfloxacin, and olafloxacin or tetrachyclines will be affected (chelation) by magnesium and aluminum antacids contained in didanosine, Hence these drugs should be given 2 hours before or 2 hours after didanosine is given.

Laboratory value alterations
The values for alanine aminotrasferase (ALT/SGPT), Alkaline phosphatase, Aspartate aminotransferase (AST/SGOT) Bilirubin (serum), serum amylase, serum lypase serum triglycerides and serum uric acid may be increased.
Serum Potassium may be decreased - it may be secondary to diarrhea from the buffer rather than to didanosine itself.

Medical considerations
Risk benefit should be considered when the following medical problems exist: -

- Alcoholism, active or
- Hyper triglyceridemia, or history of or
- Pancreatitis, or history of
- Conditions requiring -sodium restriction, such as cardiac failure, cirrhosis of the liver or severe hepatic, hypertension, renal function impairment, or toximia of pregnancy (because didanosine tablet or powder for oral solution contains sodium).
- Gouty arthritis - because didanosine increases uric acid.
- Phenylketonurea
- Peripheral neurpathy.

Side/Adverse Effects

Differentiation between the side effects of didanosine therapy and severe (complications) of HIV may be difficult, because of similarity of effects.

More frequent incidences that seek medical attention include peripheral neuropathy where as less frequent incidence is pancreatitis.

Cardiomyopatahy, hepatologic toxicity (anemia, granulocytopenia, leukopenia or thrombocytopenia), hepatitis, hypersensitivity retinal depigmentation and seizures are rarely observed. Incidence that are frequent & indicate medical attention only if they continue or are bother some include CNS toxicity dryness of mouth and GI disturbances.

Patient consultation

Before using this medication - check conditions affecting use: use in children may cause retinal depigmentation, which is more likely to occur in children receiving doses above 300 mg/m^2 per day.

Other medications, especially other drugs associated with pancreatitis and peripheral neuropathy, or medications that require acidic environment for absorption.

Other medical problems - alcoholism, hypertriglyceridemia, pancreatits or a history of pancreatitis, conditions requiring sodium restrictions, or peripheral neuropathy.

Proper use of this medication: -

- Importance of not taking more medication than prescribed; importance of not discontinuing medication without checking with physician; discontinuing medication and calling physician at first signs and symptoms of pancreatitis (abdominal pain, nausea and vomiting).

- Importance of not missing doses and of taking at evenly spaced times.

- Proper administration: -
  For buffered didanosine for oral solution

  Preparing by opening the packet and dissolving its contents in ½ glass (4 ounces) of water. The powder should not be mixed with fruit juice or other acid-containing liquid. Stirring the mixture for approximately 2 to 3 minutes until the powder is completely dissolved. Swallowing the entire solution immediately.

  For tablets

  Patients older than 1 year of age must take 2 tablets at each dose to provide adequate buffering and to prevent gastric acid degradation of didanosine.

  Children 1 year of age should receive a tablet dose. The recommended dose for children is based on body surface area and, for adults, on body weight. Thoroughly chewing, manually crushing, or dispersing in at least 1 ounce of water prior to consumption. Because the tablets are hard, they may be difficult to chew for some patients; manually crushing or dispersing the tablets may be preferable. To disperse tablets, 2 tablets should be added to at least 1 ounce of drinking water. The mixture should be stirred until a uniform dispersion forms and consumed immediately.

- Proper Dosing Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses.

- Proper storage

General Dosing Information
Two tablets must be taken at each dose by patients older than 1 year of age to provide adequate buffering and to prevent gastric acid degradation of didanosine. Children under 1 year of age should receive a tablet dose. The recommended dose for children is based on body surface area and, for adults, on bodyweight.
It is recommended that patients on hemodialysis receive their dose of didanosine after dialysis

Diet/Nutrition
All didanosine formulations should be taken on an empty stomach. Administration with food

decreases absorption by approximately 50 %. Patients on sodium restricted diet should be made aware that this medicine contains sodium.

Patients with phenylketonuira should be made aware that didanosine tablet contains varying amount of phenylalanine.

Bioequivalence - didanosine tablets are 20 to 25 % more bioavailable than the buffered powder for oral solution. Because of this, the dose of the tablets is correspondingly lower and the dosing of the two products can not be interchanged.

Buffered Didanosine for oral solution

Usual adult and adolescent dose : -

oral - patients weighing <60 Kg - 167 mg every twelve hours

- patients weighing ≥60 Kg - 250 mg every twelve hours

This, product is usually not prescribed for small children.(See didanosine for buffered oral suspension or Didanosine tablets).

Packaging and Storage

Store below 40°C(104°F) preferably between 15 and 30°C (59 and 86°F), unless otherwise specified by the manufacturer.

Stability : After preparation, the solution may be stored at room temperature for up to 4 hrs.

Incompatibility - Didanosine is unstable in acidic solutions and should not be mixed with fruit juice or other acid - containing liquid.

Auxiliary Labeling -

- Dissolve contents of packet in one-half glass (4ounces) of water
- Continue medicine for full time of treatment
- Take on empty stomach.

Didanosine for Buffered oral suspension

- This product is usually not used by adults and adolescents (see buffered didanosine for oral solution)

Usual pediatric dose:

- Body surface area up to 0.4 m^2 - 31mg (3 ml) every 8 to 12 hours
- Body surface area up to 0.5 to 0.7 m^2 - 62mg (6 ml) every 8 to 12 hours
- Body surface area up to 0.8 to 1.0m^2 - 94mg (9.5 ml) every 8 to 12 hours
- Body surface area up to 1.1 to 1.4 m^2 - 125 mg (12.5 ml) every 8 to 12 hours

Packaging and Storage:-

Prior to reconstitution, store below 40°c (104°F), preferably between 15 and 30 °c(59 and 86 °F), unless otherwise specified by the manufacturer

Preparation of dosage form

Didanosine pediatric powder must initially be diluted by adding 100 ml or 200 ml of purified water to the 2000 mg or 4000 mg bottle of powder, respectively. This produces an initial concentration of 20 mg per ml. This solution must be further diluted as follows:

One part of 20 mg per ml solution should be mixed immediately with one part of an aluminium and magnesium containing antacid. This provides a final dispensing concentration of 10 mg per ml.

For home use, the solution should be dispensed in an appropriately sized, flint - glass bottle with child-resistant closure.

Stability

After reconstitution, the solution may be stored up to 30 days in the refrigerator (2 to 8°c). Unused portion should be discarded after 30 days.

Auxiliary labelling

- Refrigerate
- Shake well
- Continue medicine for full time of treatment
- Beyond-use date
- Take on empty stomach

Note - When dispensing, include a calibrated liquid - measuring device.

Didanosine Tablets (oral)

Usual adult & adolescent dose

- Patients weighing <60 Kg - 125 mg every 12 hours
- Patients weighing ≥ 60 Kg - 200 mg every 12 hours

Usual Pediatric dose

Body surface area	Dose to be given every 8 t0 12 hours
Upto0.4 Sq.meter	25mg
0.5 - 0.7 Sq.meter	50mg
0.8 - 1.0 Sq.meter	75mg
1.1 - 1.4 Sq.meter	100mg

Packaging and Storage

Store below 40°c (104°F), preferably between 15 and 25°c (59 and 86°F), unless otherwise specified by the manufacturer.

Stability - If dispersed in water, the solution may be stored for up to 1 hour at room temperature.

Auxiliary labeling

- Continue medicine for full time of treatment
- Do not swallow tablets whole
- Take on empty stomach

Nevirapine

Nevirapine is a non-nucleoiside reverse transcriptase inhibitor (NNRTI) (approved in 1996), non-competitively inhibit HIV reverse transcriptase by binding a site distant from the active site involved in genomic replication.

Nevirapine monothrapy results in the rapid emergence of resistant HIV. Therefore, it should always be given in combination with at least one other antiretroviral agent.

HIV-2 reverse transcriptase and eukaryotic DNA polymerases are not inhibited by nevirapine.

Pharmacokinetics

Mechanism of action – see for the NRTIs group.

Absorption

Readily absorbed. Bioavailability was 93 % for single – dose administration of a 50 mg tablet and 91 % for a single – dose administration of a 50 mg oral suspension. Nevirapine may be administered with or without food.

Distribution

Highly lipophyllic and widely distributed.

It crosses the placenta and is distributed into breast milk.

Concentrations in the CSF (n=6) were 45 % of those seen in plasma, which is a ratio that is approximately equal to the fraction not bound to plasma protein.

Protein binding - moderate (60 %)

Biotransformation – Extensive oxidative metabolism by the cytochrome P450 enzyme system to several hydroxylated metabolites.

Half-life – Approximately 45 hrs after a single dose, and 25 to 30 hrs following multiple dosing with 200 to 400 mg per day.

Time to peak concentration – 4 hrs after a single 200-mg dose.

Elimination

Renal – approximately 91 % of a radio labeled dose was recovered in the urine, with 80 % of that made up of glucuronide conjugates of hydroxylated mentalities. Less than 5 % of the recovered radio labeled dose was made up of the parent drug.

Fecal – approximately 10 % of a radio labeled dose was recovered in the feces.

Precautions to consider

Breast-feeding – Nevirapine is distributed into the breast milk.

Drug Interactions and/or Related Problems

Nevirapine is an inducer of cytochrome P450 enzymes, particularly CYP3A. Auto induction occurs with Nevirapine and it has been found to increase the apparent oral clearance by 1.5 to 2 times as treatment continues from a single dose to multiple dosing at 2 to 4 weeks. Auto induction also results in a decrease in the terminal half-life of nevirapine from 45 hours after a single dose to approximately 25 to 30 hrs after multiple dosing with 200 to 400 mg per day. Medications that are metabolized by CYP3A should be monitored carefully when they are administered concurrently with nevirapine.

Cimetidine - known inhibitor of C4P3A -- increase steady state concentration of Nevirapine.

Contraceptives, estrogen containing, oral
Induction of CYP3A by nevirapine ---decrease concentration of oral contraceptives.
Didanosine or Zalcitabine or Zidovudine
Ketoconazole - Nevirapine reduces plasma concentration of Ketoconazole.
Macrolide antibiotics - (similar way as cimetidine)
Protease inhibitors such as: Indinavir, Ritonavir, Saquinavir (similar mechanism as oral contraceptives)

Rifabutin or Rifampin
These drugs induce CYP3A --- plasma concenteration of nevirapine decreases.

Laboratory value alteration: -
Alanine aminotrasferase (ALT, SGPT), serum and
Aspartate aminotransferase (AST, SGOT), serum and
Gamma - Glutamyltransferase (GGT) values maybe increased; hepatitis has been reported occasionally.

Risk-benefit should be considered when hepatic and renal function impairment exists.

Side /Adverse effects

Severe and life-threatening skin reactions, including Stevens - Johnson Syndrome and toxic epidermal necrolysis, have occurred in patients taking nevirapine. It usually occurs within the first 6 weeks of therapy. Nevirapine must be discontinued immedi- ately in patients who develop a severe rash or a rash accompanied by constitutional symptoms.

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis, has been reported. Some of these cases began in the first few weeks of therapy, and some were accompanied by rash. Nevirapine treatment should be interrupted in patients who develop moderate or severe liver function test abnormalities until they return to normal values. Nevirapine should be discontinued if liver function abnormalties recur up on the resumption of therapy.

Incidence more frequent is Granulo- cytopenia (usually in children), skin rash (mild to moderate maculopapular erythematous eruption with or without itching, (located primarily on the trunk, face and extremities). GI effects (abnormal or stomach pain, diarrhea, nausea) and headache. Less frequent incidence include - Fever, hepatitis (yellow skin or eyes); ulcerative stomatitis (sores or ulcers in the mouth).

Patient consultation

Conditions to be considered include - Hypersensitivity to Nevirapine, pregnancy, breast-feeding (nevirapine is distributed into breast milk), use in children (Granulocytopenia occurs more frequently in children) other medications - especially estrogen - containing oral contraceptives, ketoconazole, Protease inhibitors, and rifampicin. Other medical problems especially, hepatic function impairment.

Proper use of this medication -

- ❖ Nevirapine may be taken with or without food.
- ❖ Importance of not taking more medication than prescribed,
- ❖ Importance of not discontinuing nevirapine without checking with phypsician
- ❖ Compiance with full course of therapy
- ❖ Importance of not missing doses and taking doses at evenly spaced times
- ❖ Not sharing medication with others

Proper dosing
Missed dose: taking as soon as possible; not taking if almost time for next dose, not doubling doses.

General dosing Information
Nevirapine therapy is initiated with a 14-day period of 200 mg per day before increasing the dose to 400 mg/day. This has been found to decrease the incidence of rash, which can be severe and life threatening. Rash usually occurs within the first 28 days of therapy. The dose of nevirapine should not be increased to 400 mg/day until the rash has resolved. Nevirapine must be discontinued immediately in patients who develop a severe rash or a rash accompanied by constitutional symptoms.

Nevirapine therapy should be interrupted in patients that develop moderate or severe liver function test abnormalities. Therapy must be restarted with a 14 day period of 200 mg /day before increasing the dose to 400 mg per day when liver function test return to base line. Nevirapine should be discontinued permanently if moderate or severe liver function abnormalities recur.
Patients who interrupt nevirapine therapy for more than seven days should restart dosing with 200 mg once a day for the first 14 days, then increase the dose to 200 mg twice a day. Nevirapine oral suspension and tablets are bioequivalent and interchangeable at doses of up to 200 mg.

Usual adult dose:
Oral - 200 mg (Nevirapine base) once a day for the first 14 days, then 200 mg twice a day in combination with other antiviral agents.

Usual paediatric dose:
Infants 2 months to 8 years - oral 4 mg (base)/Kg body wt once a day for 14 days, then 7 mg/Kg body wt two times a day in combination with other antiretroviral agents.

Children 8 years of age and older: Oral, 4 mg (base) per Kg of body weight once a day for 14 days, then 4 mg/Kg of body weight two times a day, in combination with other antiretroviral agents.

Packaging & Storage - store between 15 and 30^{o}c (59 & 68^{o}F)
Auxiliary labeling- take for full time of treatment
-Does not require refrigeration

INDINAVIR

Indinavir is a protease inhibitor (PI), HIV isolates with reduced susceptibility have been recovered from some patients treated with it. Resistance correlated with the accumulation of mutations that resulted in the expression of amino acid substitutions at eleven residue positions in the viral protease.

Cross-resistance between indinavir and reverse transcriptase inhibitors is thought to be unlikely because they affect different enzyme targets. However cross-resistance was observed between indinavir and ritonavir, another protease inhibitor. Varying degrees of resistance have been noted between indinavir and other protease inhibitors.

Pharmacokinetics

Mechanism of action – see for the PIs group.
Absorption: -

Readily absorbed when taken on an empty stomach. Administration of indinavir with a meal high in calories, fat, and protein resulted in an 84 % reduction in peak plasma concentration

(C_{max}) and a 77 % reduction area under the plasma concentration - time curve (AUC). Administration with a lighter meal resulted in little or no change in C_{max} or AUC.

Protein binding - moderate, 60 %
Biotransformation
Hepatic: Seven metabolites have been identified, one is a glucuronide conjugate and six are oxidative metabolites, Cytochrome P450 3A4(CYP3A4) has been found to be the major enzyme responsible for formation of oxidative metabolites.

Half-life-Approximately 1.8 hour
Time to peak concentration - Approximately 8 hour after administration in the fasted state.
Elimination - Fecal (majority), Renal (only some part)

Drug Interactions and/or related problems:
Competition for CYP3A4 by indinavir could result in inhibition of the metabolism the following medications and elevated plasma concentration Astimazole, cisapride, midazolam, Terfenadine, Triazolam. ⇒ There is a potential for serious and/or life-threatening side effects, concurrent use of indinavir with any of these medications is not recommended.

Cimetidine, Clarithromycin, estrogen - containing oral contraceptives, Didanosine (for optimal absorption indinavir seeks acidic P^H while didanosine degraded by Acidic PH).
Fluconazole decrease AUC while ketoconazole results in an increase in the AUC of indinavir.

Grapefruit juice - decrease in AUC of indinavir, Isoniazid, Lamivudine, Zidovudine, Quinidine.
Rifabutin - Coadminstration results in an increase of AUC of both drugs.
Rifampicin - is potent inducer of CYP3A4, which could significantly decrease the plasma concentration of indinavir, concurrent use with indinavir is not recommended.
Stavudine and Sulfamethoxazole + Trimaethoprim, though dosing modification is not required, indinavir affects AUC of these drugs.

Side/Adverse Effects

Incidence more frequent - kidney stones manifested as blood in urine & sharp back pain just below ribs; this may need medical attention - Hydration and temporary interruption of therapy.

Asthenia(generalized weakness), GI disturbances, headache, insomnia, taste perversion.

Incidence less frequent - Dizziness, Somnolence, diabetes or hyperglycemia, Ketoacidosis (confusion, dehydration, fruity mouth odor, dry or itchy skin).

Patient consultation
Conditions affecting use include - Hypersensitivity to indinavir, pregnancy, breast feeding, concurrent use of the above mentioned drugs, other medical problems like hepatic impairment.

Proper use of indinavir

- Importance of taking with 1 hr before or two hrs after a meal; it may also be taken with other liquids (skim milk, juice, coffee or tea) or with a light meal.
- Importance of drinking at least 1.5 liters of liquids over each 24 hour period.
- Importance of not taking more medication than prescribed, importance of not discontinuing indinavir without checking with physician.
- Compliance with full course of therapy.
- Importance of not missing doses and of taking at evenly spaced times. Not sharing medication with others.

Proper dosing.

Missed dose: Taking as soon as possible, not taking if almost time for next dose; not doubling doses.

Proper storage - Indinavir capsules are sensitive to moisture.

Indinavir should be stored and used in the original container and the desiccant should remain in the bottle.

- Regular visits to physician for blood tests and monitoring of blood glucose concentrations + avoiding to take other medications without consulting physician are important points to consider.

General Dosing Information: -

The recommended adult dose of indinavir is 800-mg base every 8 hours (To prevent kidney stones it is advisable to take plenty of water). Patients with mild to moderate hepatic function impairment due to cirrhosis require a dosage reduction 600 mg base every 8 hours.
For pediatric use: safety and efficacy have not been established.

Packaging and storage
Store at room temperature, preferably between 15 and 30^{o}c (59 and 86^{o} F). Store in a tight container, protect from moisture.

Auxiliary labeling

- ❖ Take on an empty stomach
- ❖ Continue medication for full time of treatment
- ❖ Do not take other medications without physician's advice.

SAQUINAVIR

Saquinavir is HIV protease inhibitor (PI) Cross-resistance between saquinavir (following prolonged [24 + 27] weeks) treatment with saquinavir mesylate capsules and other HIV PIs such as indinavir, nelfinavir, and ritonavir may be observed. However, cross - resistance between saquinavir and reverse transeriptase inhibitors is thought to be unlikely because they affect different parts of HIV replication.

Pharmacokinetics

Absorption: -

Saquinavir mesylate capsule -
Average approximate for absolute bioavailability is 4 % (range 1 to 9 %), who receive a single 600 mg dose following a high - fat meal, low bioavailability was thought to be due to incomplete absorption and extensive first pass metabolism. The area under the plasma concentration time curve (AUC) and peak plasma concentration (Cmax) values were 2.5 times higher in HIV infected patients following multiple dosing than after a single dose, HIV infected patients has AUC and Cmax values that were approximately twice those of healthy volunteers when both groups were administered the same treatment regimen. Administration of saquinavir with a high fat meal increased the AUC and Cmax to approximately twice the concentrations seen following administration with a low caloric, lower fat meal. The effect of food persisted up to 2 hours.

Saquinavir soft gelatin capsules
The bioavailability of the soft gelatin capsule formulation was estimated to be 33.1 % of that of the original saquinavir mesylate capsule formulation. An increase in the plasma concentration of saquinavir was observed in HIV - infected patients than healthy volunteers when both are given the soft gelatin capsule.

Protein binding - very high 98 %
Biotransformation:-

Hepatic - over 90 % of saquinavir is metabolized by the cytochrome P450 isoenzyme CYP3A4. Saquinavir is thought to undergo extensive first - pass metabolism and is rapidly metabolized to a variety of inactive mono - and di - hydroxylated compounds.

Elimination
Fecal - Approximately 88 % of orally administered saquinavir is eliminated fecally as unchanged saquinavir and metabolites within 48 hours of dosing.
Renal - Approximately 1 % of orally administered saquinavir is eliminated unchanged in the urine within 48 hours of dosing.

Drug Interactions and Related problems

Concurrent use of saquinavir with terfenadine has resulted in an increase in the plasma concentrations of terfenadine; competition for the cytochrome P450 enzyme CYP3A by saquinavir may also inhibit the metabolism of astemizole, cisapride, ergot derivatives, midazolam, or triazolam, calcium channel blocking agents, clindamycin, Dapsone, Quinidine - due to the potential for serous and/or life - threatening cardiac arrythmias or prolonged sedation, concurent use of these drugs with saquinavir is not recommended.

Carbamazepine, Dexamethasone, phenobarbital, phenytoin, Rifabutin/ Rifampicin or other medications that are metabolic inducers of the cytochrome P450 enzyme system may reduce AUC and peak plasma concentration (Cmax) of saquinavir, use of alternative medications should be considered if patients are taking saquinavir,

Delavirdine - concurrent use resulted in a five fold increase in the AUC for saquinavir mesylate capsules.
Concurrent administation of indinavir, Nelfinavir, or Ritonavir increases in the AUC of saquinavir.
Clarithromycin and Ketoconazole, also increase AUC and Cmax of saquinavir if administered together.

Laboratory value alterations

Serum Alanine Aminotransferase (ALT, SGPT), Amylase, Aspartate Aminotrase (AST, SGOT), creatinine Kinase (CK) or Gamma - glutamyltransferase values may be increased. Bilirubin or potassium concentrations may be increased. Plasma glucose concentrations may be decreased or increased. Close monitoring of patient's plasma glucose concentrations is recommended; development of hyperglycemia or diabetes may be associated with the use of protease inhibitors.

Contraindications

Hypersensitivity to saquinavir, hemophilia, hepatic function impairment.

Side /Adverse effects

Saquinavir is indicated in combination with other antiretroviral agents. Saquinavir was not found to alter the pattern, frequency, or severity of toxicities associated with NRTIs. Most side effects were considered to be mild.

Less frequently, Asthenia (weakness) & GI disturbances, where as rarely Diabetes oralhyperglycemia, ketoacidosis (manifested as confusion, dehydration fruity mouth odour, nausea, vomiting, and weight loss), Paresthesia (burning or pricking sensation) skin rash, and head ache may be experienced.

Patient Consultation

Before taking Saquinavir.
Conditions affecting its use, especially:

- Hypersensitivity to saquinavir
- Breast feeding- it is not recommended that HIV infected mothers do not breast feed to avoid potential postnatal transmission of HIV to an uninfected infant.)
- Contra indicated drugs and disease conditions mentioned above should also be considered.

Proper use of Saquinavir:-

- Importance of taking saquinavir with a meal or with in 2 hours after a meal.
- Compliance with full course of therapy.
- Importance of not missing doses and of taking at evenly spaced times. Not sharing medication with other.
- Regular visit to physician for blood tests and monitoring of blood glucose concentrations.
- Proper dosing

  Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses.

Dose: -
The dosing and strength of the dosage forms available are expressed in terms of saquinavir base.

Safety and efficacy have not been established for children under 16 years of age.
Saquinavir is given orally and available in two dosage formulations.

a. Saquinavir soft gelatin capsule
Usual adult dose - 1200 mg three times a day with a meal or within 2 hours of eating a meal, in combination with other appropriate antiretroviral agents.

Packing and storage:
Store in a refrigerator between 2 & 8^{o}c in a tight container.

Stability - capsules stored in a refrigerator remain stable until the expiration date printed on the label capsules that are brought to room temperature (25^{o}c) are stable for up to 3 months.

Auxiliary Labeling
- Refrigerate
- Continue for full time of treatment
- Take with food
- Do not take other medications without physician's advice

b. Saquinavir mesylate Capsules
Usual adult dose - 600 mg (base) three times a day within two hours after a meal, in combination with other appropriate antiretroviral agents.

Packing and storage
Store between 15 and 30^{o}c(59 & 86^{o}F) in a tight container

Auxiliary labeling: -
- Continue for full time of treatment
- Take with food

Do not take other medications with out physician's advice.

Training Course On Good Manufacturing Practice (GMP) For Inspectors And Manufacturers

A one-week training program on Good Manufacturing Practice had been conducted by DACA in collaboration with WHO in Nazarath, Pan Afriqe Hotel, from 3rd-8th, June, 2002.

The training was given for 40 professionals from 10 manufacturers and 6 Inspectors from DRUG ADMINISTRATION AND CONTROL AUTHORITY (DACA).

Opening the training, Ato Mengisteab W/Aregay stated that the objective of the training is to improve manufacturing discipline in pharmaceutical manufacturers so as to produce drugs of good quality, safety & efficacy. He also said that the numbers of manufacturing plants in our country are increasing and currently there are 10 plants. Hence, professionals from these manufacturers and the inspectors in the regulatory Authority have to up date their knowledge concerning current good manufacturing practice for materializing the stated objectives.

The trainer of the course includes Mr. Kuwana & Ato Eshetu Wondemagegnehu from WHO and Ato Mengisteab W/Aregay & Ato Bekele Tefera From DACA.

Some of the important topics included in the training are Principles of effective Regulation, Quality Management, Sanitation and Hygiene, Documentation, SOP, IP forms and Batch records, Post-marketing activities, counterfeit and substandard medicines and so on were included in the training.

The participants divided in four groups and discussed the current problems encountered in following GMP guideline by pharmaceutical Manufacturers and DACA. The absence of trained manpower in the country, lack of incentives, very low salary, poor attention of the manufacturers to follow GMP guideline were raised as a major problems in all groups. Particularly the absence of sufficient trained manpower was the hot issue in the discussion of all groups.

All groups suggested DACA, WHO, professional associations and NGOs are the responsible bodies to alleviate the stated problems. They also pointed that there must be sustainable training programs to professionals because the inspectors and the professionals in the manufacturers' to be inspected needs to update their knowledge on GMP.

The participants were given certificate for their successfully attending the training by vice minister of health, Dr. Demissie Tadesse.

Finally, the course participants for practical demonstration purpose have visited two pharmaceutical manufacturing plants and this created very good chance to share experience among professionals.

The training materials were relevant to the participants' work, the content and materials were well presented, and the program was well run. Generally, the training was an enjoyable and active course that was thoroughly appreciated by the participants.

Legislation workshop conducted/ Nazareth.

A three-days workshop from 2nd - 4th Sept 2002 was organized by DACA to discuss on legislation of Drug Administration and control. Participants were delegates from Health and Agriculture bureaus of the nine regional states and the DireDawa Administrative council, representatives of Ethiopian Pharmaceutical Association (EPA), Ethiopian Druggists' Association, Vet. Professionals Association, Professionals from pharmaceuticals importer and distributors and retailers, along with professionals from the Authority (DACA). Total of 80 participants divided into four groups discussed each and every point on the draft of the legislation and two guide lines (Establishing and working guideline of pharmaceutical import & distribution and Retail out lets). There was live argument and different ideas, comments and

suggestions were raised, examined and discussed.

On the closing of the workshop the General manager, Ato Hailesilassie Bihon appreciated the in put of the participants and emphasized that contravention is obstacle whereas working hard hand-in-hand with harmony and dedication is an important factor for growth and development of the sector in particular and the country (Nation) in general. On the other hand he also noted that, DACA is government office and everyone is there to serve the public and its door is open to everyone who came for service or to give comment that will improve the sector.

Training on Rational use of NPS drugs Conducted!!!

Training on the rational use of Narcotic Drugs and Psychotropic Substances was given for health professionals working in different health institutions of Addis Ababa from August 26 to 29, 2002 at Adama Mekonnen Hotel, Nazareth. Sixty health professionals, namely, physicians, pharmacists, druggists, pharmacy technicians and nurses working in public, private and NGO hospitals, health centers ,Addis Ababa City Administration Health Bureau, pharmaceutical importers and distributors participated the training.

The objective of the training was to increase the awareness of health professionals about the importance special control and proper utilization of narcotic drugs and psychotropic substances. In addition to strengthening the control system on the import, distribution and consumption, the training also aimed at improving the availability of these drugs for needy patients by visualizing the role of NPS drugs in the health care delivery. Besides, the need for narcotic drugs in pain management was also emphasized, as the consumption of these drugs is decreasing in the country from time to time though the real demand was increasing.

The goal of the training is promoting rational use of narcotic drugs and psychotropic substances and the training was finalized by preparing plan of action for promoting rational use of narcotic drugs and psychotropic substances.

Official Launching of special Pharmacy Project

The establishment of special pharmacies, nation wide, in 150 government health facilities was officially launched on 25th of July 2202, in a half day meeting at Ghion Hotel hear in Addis in the presence of Dr. Demise Tadesse, vice minister of health and Ms. Mary Lewellen, Director, USAID. The ceremony was attended by head of Regional Health Bureaus, Pharmacists of Regional Health Bureaus, MOH and DACA department heads and invited guests from UNICEF and WHO.

The health care finance of the MOH and ESHE/JSI/ Abt project organized the launching program.

At the ceremony it was pointed out that the special Pharmacy Project has emanated consequent to the problems observed due to scarcity of government annual allocated budget to ensure sustainable supply of drugs, medical supplies and instruments. Special Pharmacies are Pharmacies operating in the health facility with a revolving fund obtained from sources other than the government allocated recurrent budget. The main objectives of which are: i) make essential drugs available in a sustainable manner; ii) helps stabilize and regular the market price; iii) generate surplus that will be utilized to motivate staffs, purchase diagnostic facilities, medical equipment and other supplies that are necessary to bring and improve the quality of services provided in the facility the gap of the recurrent budget allocated from the government.

The special pharmacies will start operation with seed fund of USD 1.12 million donated from USAID. There after, this seed fund will revolve at the facility it self to help purchase drugs and medical supplies from local suppliers.

The special pharmacies will operate as per the guideline on management and operation of special pharmacies.

VET DRUGS EVALUATION AND REGISTRATION GUIDE LINE WORKSHOP CONDUCTED

A workshop on Veterinary Drug Evaluation and Registration Guide- line was organized by Drug Administration and Control Authority, at Global Hotel on July 5-6,2002. Seventy-four participants representing different institutions were attended the two days workshop.

The objectives of the workshop were to:-

1. High light participants on the concept of drug registration and quality assurance.

2. Introduce participants with the draft document of Guideline for the registration of veterinary products (pharmaceuticals) in Ethiopia.

3. Propose idea necessary to bring better registration service.

The goal of the workshop was to attain its objective and to develop idea on vet pharmaceutical registration guideline. The Participants discussed on draft document of the registration guideline of vet. Pharmaceutical products prepared by DACA. Participants forwarded invaluable constructive comments and DACA would like to acknowledge all participants on this regard.

Besides, Topics like National drug policy & proclamation, National drug evaluation system, and Distribution of livestock diseases and provision of safe effective and quality vet drugs was presented.

Participants of GMP training

CALLS FOR ADR REPORT

Any drug may produce unwanted or unexpected adverse reactions. Detection and reporting of these reactions is of vital importance.

Taking this in to consideration, we would like to draw the attention of our readers that an adverse drug reaction monitoring and promotion control division has been established within drug administration and control authority (DACA).

Physicians, Health officers, Dentists, and pharmacists are encouraged to report suspected reactions to any therapeutic agent including drugs, blood products, vaccines, x-ray contrast media, dental and surgical materials, uterine device and contact lens fluids.

The adverse drug reaction monitoring and promotion control division would like to call upon health professionals to report all suspected adverse events, however minor, for new drugs and all serious suspected reactions including those that are fatal, life-threatening, disabling, incapacitating, or which result in prolonged hospitalization for established drugs.

To facilitate reporting, the division has prepared postage service prepaid reporting form (See Annex) and reporting guideline, which will be available at each health institution. If you need copies of the form or have an ADR case to report, please mail all ADR correspondence to the following Address:

Drug Administration And Control Authority Of Ethiopia

P.O.Box 5681

Addis Ababa

Ethiopia

METAMIZOLE

Analysis of Swedish adverse reaction reports

Metamizole (Dipyrone) is an analgesic compound structurally related to amidopyrine from the phenylpyrazole group. In the early 1930s, amidopyrine was identified as a cause of agranulocytosis. Soon after metamizole was also associated with agranulocytosis and the risk was suggested to be about 1 in 120 treated patients. This estimate however appeared to be based on potentially biased information from published and unpublished patient series. Because of the risk of agranulocytosis, metamizole has been banned or withdrawn from the market in most industrialized countries but is still available in some countries in Europe including Germany France and Spain, the far East, Africa and Latin and South America. Of particular intrigue are the Swedish regulatory measures for metamizole. In Sweden all metamizole containing products were first withdrawn in March 1974 due to an estimated incidence of agranulocytosis of 1 in 3000 patients. However, later, data from the International Agranulocytosis and Aplastic Anemia (IAAA) study put down the risk for agranulocytosis as low as 1.1 cases per million users. Therefore, in September 1995, metamizole was reapproved based on the results from the IAAA study and then later, again suspended in April 1999 based on Swedish adverse drug reactions data, which have now been published. Dr. Karin Hedenmalm from the Swedish Medical Products Agency and Dr Olav's University Hospital have reviewed all reports of metamizole - related blood dyscrasias that were submitted to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC). Based on pharmacy sales data and spontaneous reporting of blood dyscrasias in Sweden, they estimate that the risk of agranulocytosis related to metamizole (Dipyrone) appears to be at least 1:1439(95 % confidence interval 1:850, 1! 4684) prescriptions, a much higher figure than previously estimated. Ninety two percent of the cases of blood dyscrasias occurred during the first 1 months of treatment. Additional risk factors were identified in 36 % of the patients. In addition, they report that agranulocytosis was not the only manifestation of metamizole-induced blood dyscrasias; in some of the cases all three haematopoiesis were affected according to bone marrow sample findings. In these cases, the outcome was significantly poorer. Thus the risks of agranulocytosis from the present report seem to be considerably higher than the previously estimated risks from the IAAA study. The authors identify several possible reasons for this difference. For example, in countries where metamizole has been available for several years, the number of susceptible will decrease because individuals who develop agranulocytosis will discontinue the offending drug. In contrast count rid such as Sweden have a greater population of treatment naive individuals. The criteria of fever as a measure of agranulocytosis in the IAAA study also might have affected the choice of cases. Anybody taking metamizole for fever (and not just pain) would therefore not be included as cases in that study. Besides, an unknown proportion of agranulocytosis cases were not included in the IAAA study because the patients either recovered or died before hospital admission. Thus, the differences may be more representative of methodological gaps and do not necessarily represent different result
The present publication provides evidence for the claim of a high risk of agranulocytosis with metamizole in Swedish patients. The study does not, however, clarify whether Scandinavians are genetically at a greater risk for such reactions. Comparative studies in various countries with more diverse population could help resolve the issue further and until this data is available, other drugs should be considered as first-line analgesics.

Adopted from: WHO Pharmaceutical Newsletter No. 3, 2002

Recommendations for Effective Drug Regulation

WHO has released in 2002 a multicountry study carried out by the WHO Essential Drugs and Medicines Policy unit (EDM) that was conducted by sauwakon Ratanawijitrasin and Eshetu Wondemagegnehu. Ten countries, Australia, Cuba, Cyprus, Estonia, Malaysia, Netherlands, Tunisia, Uganda, Venzucla and Zimbabwe were considered for the study and the finding was published published as a book. The book mentions different important ideas, here the recommendations for effective drug regulation is taken from it can be seen as follows:-

- A clear sense of the mission of the regulatory authority is important in motivating DRA staff to pursue regulatory processes in order to achieve drug regulation. Governments should state clearly the mission and objectives can be easily assessed.

- Drug laws should be sufficiently comprehensive, covering all activities involving drug products and information, and updated regularly.

- One central agency should be accountable for the overall effectiveness of drug regulation.

- personnel engaged in drug regulation should be individuals of integrity and appropriately trained and qualified. Homan resources development programmes should be made available to help staff to improve their knowledge and skills and to enable them to cope with developments in pharmaceutical science and technology. They should also have access to the latest scientific and technological information to facilitate their work.
- appropriate standards and guidelines should be developed and used as tools for the application of all regulatory processes. They should be freely available to all stakeholders, including the public, in order to increase the transparency of the DRA's operations. The same standard of regulation should be applied to all drugs, whether they are imported and/or manufactured by the public or the private sector, and destined for domestic consumption or for export.

- Sustainable financing is essential to promote effective drug regulation. Drug regulatory authority financing should strike a balance between fees covering the full cost of services and government support. Fees should provide increased revenue to the authority so that it can perform effectively, and serve to discourage clients from "flooding" the system with applications that do not meet official requirements.

- Every regulatory function contributes to ensuring the safety quality and efficacy of drugs. The action taken by the authority should cover all drug regulatory functions in a balanced fashion. Support for drug regulation should not be compromised by other non-regulatory tasks with which the DRA may also be charged.
- The regulatory process should be systematically monitored in order to identify problems and determine whether actual activities match the intended actions. Moreover, the DRA should become a learning organization; which routinely conducts self-assessment and continuous quality improvement. There should be administrative and legislative supervision in order to guarantee accountability. Peer review by drug regulatory authorities in other countries can serve as a means of external auditing, whereby the performance of one agency can be compared with that of its peers.

- Any inefficiency in the regulatory process delays decision-making and may lead to shortages of critically needed drugs, thus endangering human lives.

  Drug regulatory authorities should employ various strategies to increase efficiency of resource use, e.g prioritization and streamlining of the work process; job enlargement and job enrichment for regulatory staff; pooling of international information resources; and sharing and pooling of international QC resources.

- Drug regulatory authorities should communicate regularly with their clients. They should also acknowledge the right of citizens to be provided with accurate and appropriate information on drugs marketed in their country. Educating citizens about the efficacy, safety, quality and rational use of drugs will ultimately enhance the achieve- ment of regulatory objectives.

Basic Requirements For Drug Regulation

Drug regulation is a complex task, with many stakeholders and vested interests involved. For these reason there are a number of basic requirements and some of the basic ones are discussed below:

- Sound legal basis, adequate human and financial resources.
- Independence

- It must operate, and be seen to operate, in an independent, authoritative and impartial manner.

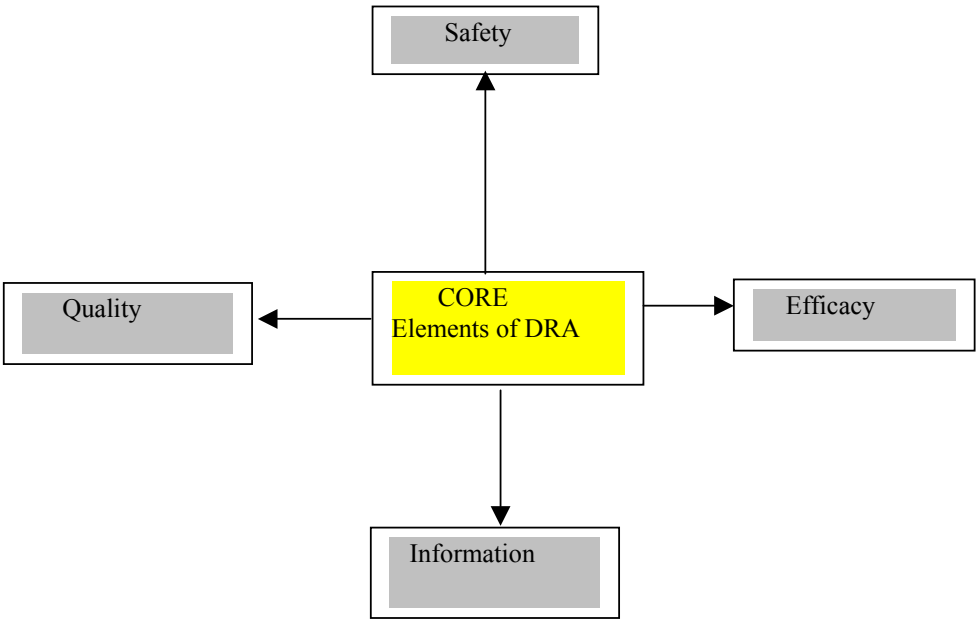
- Transparency

-One of the keys to an honest and accountable DRA is transparency in all its procedures and outcomes for all stakeholders.

  - Definition, publication and dissemination of the requirements for information to be submitted to the DRA in support of various types of applications;
  - Publication of the criteria that the DRA uses and the procedures it follows when making decisions about applications.
  - Publication of the DRA's decisions (regular comprehensive lists of drugs registered, renewals and withdrawals) and of the information upon which these are based; a DRA web site may be a convenient way to achieve this.

Adopted from: How to develop and implement a national drug policy, 2nd ed., WHO Page 48 & 49.

The main task of DRA is to ensure the quality, safety and efficacy of drugs, and the accuracy of product information.



(Photograph of lab animal on scale)

Tutorial

1. Chemical compound obtained from the roots of certain herbs belonging to the nightshade family and used to prevent motion sick ness.

   A. Digitalis B. Scopolamine C. Pyorrhea D. Streptomycin

2. Litmus, a dye used as an acid-base indicator, is made from...

   A. Lichens B. Shellfish C. Indigo plants D. Insects

3. Wide spread disease in many tropical and subtropical countries caused by the infection of the body by parasitic worms called flukes.

   A. Trichinosis B. Scoliosis C. schistosomiasis D. Hepatitis

4. This group of protozoa that are blood parasites caused African Sleeping Sickness and Chagas' disease in human beings and other animals.

   A. Filaria B. Schistosomiasis C. Tsetse D. Trypanosome

5. This group of birds inhibiting New Guinea and a few small near by islands is remarkable for including the only documented example of a poisonous bird.

   A. Bufflehead B. Pitohui C. Honey creeper D. Quetzal

(Adopted from Encyclopedia Encarta 2002)

See the answers on the next page

(Photograph at QC lab)

Answer

(Photograph at QC lab)

Adverse Drug Reaction Reporting Form

Patient's Name: (Initials only)_____ Card Nº: _____ Age: _____ Sex: _____ Weight:_____
Habit: _____ Address: _____

Adverse Drug Reaction Description (Including Laboratory test results): Date of onset of Reaction: _____/_____/_____

_____
_____
_____
_____
_____
_____
_____

Reaction necessitated: Discontinuation of drug/s/ ☐ Yes ☐ No
Prolonged Hospitalization ☐ Yes ☐ No

Information on Suspected Drug

Drug Name (use Brand Name . if generic name are used Please indicate manufacturer and batch no. if applicable.)	Route	Dose	Frequency	Date Drug		Therapeutic Indication
				Started	Stopped	
				D|M|Y	D|M|Y	
Other Drugs Taken Including self-medication						

Reaction subside after D/C of Suspected Drug ☐ Y ☐ N ☐ NA
Reaction reappear after Restart of Suspected Drug ☐ Y ☐ N ☐ NA
Treatment of reaction: _____

_____
_____
_____

Outcome: ☐ Died due to adverse reaction ☐ Died, drug may be contributory ☐ Died Unrelated to drug
☐ Not yet recovered ☐ Recovered with out sequelae ☐ Recovered with sequelae ☐ Unknown

Sequelae:

_____

Additional information: (e.g. relevant history such as allergies, chronic disease, pregnancy etc.)

_____
_____
_____

Reported by: Name _____ Profession: _____ Signature: _____ Date: _____
Name of health Institution: _____ Address: _____ Tele Nº: _____

Continued

For office use only
Received On: _____ Registration Nº: _____
Key: D|M|Y Date |Month |Year; D/C Discontinue Treatment; Y Yes; N No; NA Not available

What to report
- All suspected reactions to drugs
- Unknown or unexpected ADRs
- Serious adverse drug reactions
- Unexpected therapeutic effects
- All suspected drug interactions

From _____

_____

_____

_____

_____

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Postage
Prepaid

Drug Administration and Control Authority
ADR Monitoring & promotion control Division,
P. O. Box 5681,
Addis Ababa,
Ethiopia.