PUBLIC ASSESSMENT REPORT

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg

International Nonproprietary Name: Didanosine

Abstract

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg, supplied by Aurobindo Pharma Ltd, Plot No. 2, Maitrivihar Ameerpet, Hyderabad 500 038, Andhra Pradesh, India, was the subject of an abbreviated new drug application (ANDA) submitted to the U. S. Food and Drug Administration (USFDA) pursuant to section 505(j) of the U. S. Federal Food, Drug, and Cosmetic Act.

This ANDA was reviewed under the President’s Emergency Plan for AIDS Relief (PEPFAR). Based upon the information presented to date the USFDA concluded that Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg are safe and effective for use as recommended in the submitted labeling. The USFDA was unable to grant final approval to this ANDA at the time of review due to existing patent protection. Therefore, the ANDA was tentatively approved on July 10, 2006. This determination is based upon information available to the agency (i.e., information in the ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product.

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg, on the basis of USFDA tentative approval, were placed on the WHO Prequalification Programme list of manufacturers and suppliers whose HIV-related products have been found acceptable, in principle, for procurement by UN Agencies (Prequalification Programme: Priority Essential Medicines, 63rd Edition, 1 February 2008).

Products listed on the WHO Prequalification list with the note “USFDA” have been added to the list of products prequalified by WHO based on the scientific assessment and inspections conducted by the USFDA. Products listed as USFDA tentatively approved indicates that although existing patents and/or other marketing exclusivity prevent marketing of the products in the USA, those products meet all of USFDA’s safety, efficacy, and manufacturing quality standards required for marketing in the USA, and are eligible for purchase with PEPFAR funds.

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. Detailed conditions for the use of this product are described in the Summary of Product Characteristics (SPC), which is part of this Public Assessment Report.

The active pharmaceutical ingredient (API) of Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg is the nucleoside reverse transcriptase inhibitor (NRTI) didanosine, a well established and documented product for the treatment of HIV/AIDS in combination with other products.

Didanosine has been investigated in combination therapy in several clinical trials in both treatment-naïve and treatment-experienced patients. These studies have demonstrated significant decreases in HIV-1 viral load and increases in CD4 cell counts. Clinical endpoint data indicate
that didanosine in combination with other antiretroviral agents results in a significant reduction in the risk of disease progression and mortality.

The most commonly reported adverse events are nausea and diarrhea, dry mouth, and nervous system effects (e.g., mood changes, anxiety, headaches, difficulty sleeping). These adverse events often improve within weeks or months of starting treatment with didanosine.

The most important safety problems associated with didanosine are pancreatitis, lactic acidosis and severe liver enlargement, vision changes, and peripheral neuropathy.

The risk benefit profile of Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg, showed an acceptable safety profile and adequate antiretroviral activity.
Didanosine chewable/dispersible buffered Tablets 100mg, 150mg, 200mg
Aurobindo Pharma, Ltd.

All Accepted Presentations

<table>
<thead>
<tr>
<th>STATUS</th>
<th>INN</th>
<th>Strengths</th>
<th>Form</th>
<th>Route of Administration</th>
<th>Packaging</th>
<th>Package Size</th>
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<tr>
<td>USFDA tentative approval</td>
<td>Didanosine</td>
<td>100 mg, 150 mg, 200 mg</td>
<td>Chewable dispersible buffered tablets</td>
<td>oral</td>
<td>Bottle</td>
<td>60 tablets (all strengths)</td>
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1. **WHAT DIDANOSINE CHEWABLE/DISPERSIBLE BUFFERED TABLETS ARE AND WHAT THEY ARE USED FOR**

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg, belong to a group of antiviral medicines, also known as antiretrovirals, called nucleoside analogue reverse transcriptase inhibitors (NRTIs). These are used to treat Human Immunodeficiency Virus (HIV) infection.

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg are used in antiretroviral combination therapy for the treatment of HIV infection. Didanosine reduces the amount of HIV virus in your body and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cell that play an important role in maintaining a healthy immune system to help fight infection.

Response to treatment with Didanosine chewable/dispersible buffered Tablets varies between patients. Your doctor or health care provider will be monitoring the effectiveness of your treatment. Didanosine may improve your condition but is not a cure for HIV infection. HIV infection is a disease spread by contact with blood or sexual contact with an infected individual. Treatment with Didanosine Tablets has not been shown to reduce the risk of passing HIV infection on to others by sexual contact or by blood transfer. You must continue to take appropriate precautions to avoid giving the virus to others.

During your treatment, other infections linked to your weakened immunity (opportunistic infections) may arise. These will require specific and sometimes preventive treatment.

2. **BEFORE YOU TAKE DIDANOSINE CHEWABLE/DISPERSIBLE BUFFERED TABLETS, 100 mg, 150 mg, and 200 mg**

Do not take Didanosine Tablets if you are allergic (hypersensitive) to didanosine or any of the other ingredients of Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg (see section 6, What Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg, contain).
Take special care with Didanosine chewable/dispersible buffered Tablets

Before using this medicine, tell your doctor or health care provider if you suffer from kidney disease or liver disease (such as hepatitis)

The class of medicines to which Didanosine chewable/dispersible buffered Tablets belongs (NRTIs) can cause a condition called lactic acidosis, together with an enlarged liver. Lactic acidosis, if it occurs, usually develops after a few months of treatment. Lactic acidosis is a build up of lactic acid in the body, which can cause dehydration and coma. Deep, rapid breathing, drowsiness, and nonspecific symptoms such as nausea, vomiting, and stomach pain, may indicate the development of lactic acidosis. Lactic acidosis may also lead to rare cases of renal failure, liver failure, or fatal hepatitis.

Lactic acidosis is a medical emergency that must be treated in a hospital. If you notice any of the symptoms noted above, tell your doctor or health care provider immediately. This rare but serious side effect occurs more often in women, particularly if very overweight. If you have liver disease you may also be at greater risk of getting this condition. While you are taking Didanosine chewable/dispersible buffered tablets, your doctor or health care provider will monitor you closely for any signs of lactic acidosis.

Speak with your doctor or health care provider if you have a history of liver disease. Patients with chronic hepatitis B or C who are treated with antiretroviral agents are at increased risk for severe and potentially fatal liver adverse events and may require blood tests for control of liver function.

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, inform your doctor or health care provider immediately.

Redistribution, accumulation, or loss of body fat may occur in patients receiving antiretroviral therapy. Contact your doctor or health care provider if you notice changes in body fat.

You will need to take Didanosine Tablets every day. This medicine helps to control your condition but is not a cure for HIV infection. You may continue to develop other infections and other illnesses associated with HIV disease. You should keep in regular contact with your doctor or health care provider. Do not stop taking your medicine without first talking to your doctor or health care provider.

Taking other medicines

Tell your doctor, health care provider, or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. These may affect the action of Didanosine, or Didanosine may affect their action.

Didanosine in any form, including Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg, should not be taken in combination with stavudine and/or hydroxyurea.

Didanosine in any form, including Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, or 200 mg, may also interact with allopurinol. Didanosine and allopurinol should not be used concurrently. Didanosine in any form may interact with ribavirin, hydroxyurea, methadone,
tenofovir, indinavir, lopinavir, ritonavir, isoniazid, or zalcitabine. The use of any of these drugs along with Didanosine should be carefully considered and discussed with your doctor or healthcare provider.

Taking Didanosine at the same time with medicinal products that are potentially damaging to the kidneys (nephrotoxic) or bone marrow (drugs known as “myelosuppressive,” including pentamidine, dapsone, pyrimethamine, cotrimoxazole, amphotericin, flucytosine, cidofovir, ganciclovir, valganciclovir, interferon, vinristine, vinblastine, or doxorubicin) may increase the risk of adverse reactions to didanosine. If concomitant therapy with didanosine and any of these medicinal products is necessary, extra care must be taken in monitoring kidney or blood functions. If required, the dosage of one or more agents should be reduced.

Use of antacids containing magnesium or aluminum along with Didanosine Tablets may increase risk of adverse events associated with the antacid components.

Ketoconazole and itraconazole should be administered at least 2 (two) hours prior to dosing with Didanosine, as their absorption from the stomach can be affected by acidity levels in the stomach.

Didanosine should be administered at least 2 (two) hours after or 6 (six) hours before dosing with ciprofloxacin.

**Taking Didanosine chewable/dispersible buffered Tablets with food**

Didanosine chewable/dispersible buffered Tablets should be taken on an empty stomach, at least 30 minutes before or 2 (two) hours after eating. Do not take Didanosine chewable/dispersible buffered Tablets with food.

**Pregnancy**

If you become pregnant, or are planning to become pregnant, you must contact your doctor or health care provider to discuss the potential adverse effects and the benefits and risks of your antiretroviral therapy to you and your child.

If you have taken didanosine in any form during your pregnancy, your doctor or health care provider may request regular visits to monitor the development of your child. Such visits may include blood tests and other diagnostic tests.

In children whose mother took nucleoside and nucleotide analogues during pregnancy, the benefit from the reduced chance of being infected with HIV is greater than the risk of suffering from side effects.

**Breastfeeding**

Since the HIV virus passes into breast milk it is recommended that HIV-infected women taking didanosine in any form do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

**Driving and using machines**

No information on the effects of didanosine on the ability to drive and use machines is available.
3. **HOW TO TAKE DIDANOSINE CHEWABLE/DISPERSIBLE BUFFERED TABLETS**

Always take Didanosine chewable/dispersible buffered Tablets exactly as your doctor or health care provider has instructed you. You should check with your doctor, health care provider, or pharmacist if you are unsure or have any questions.

Take Didanosine Tablets on an empty stomach, at least 30 minutes before or 2 (two) hours after eating. Do **not** take Didanosine with food.

It is important to continue taking this medication (and other anti-HIV medications) exactly as prescribed by your doctor.

Didanosine works best when the amount of drug in your body is kept at a constant level. Therefore, take this drug at evenly spaced intervals, preferably at the same time(s) each day.

Do not take more or less Didanosine Tablets than are prescribed by your doctor or health care provider. Do not stop taking Didanosine Tablets (or any other HIV medicines) even for a short time unless directed to do so by your doctor or health care provider. Skipping or changing your dose without approval from your doctor or healthcare provider may cause the amount of virus in your body to increase, make the infection more difficult to treat (resistant), or worsen side effects.

The recommended total daily dose of Didanosine Tablets is based on body weight. Your doctor will determine your dose based on your body weight as well as your kidney and liver function, and any other factors, such as other medicines you currently take or side effects you may have had with other medicines.

Didanosine Tablets contain an antacid to reduce the amount of acid in your stomach. If you have too much stomach acid, it will cause Didanosine Tablets to break down and be less effective. However, too much antacid may cause stomach problems. Therefore, take at least two tablets but never more than four at a time.

Do **not** swallow Didanosine Tablets whole. Chew the tablets well or mix them in water. You may drop the tablets in at least one ounce of water and stir well before swallowing. If you choose to mix the tablets in water, you may add one ounce (2 tablespoons) of clear apple juice to the mixture for flavor, but do not use any other kind of juice.

Children should be assessed for the ability to swallow capsules or tablets. If a child is unable to reliably swallow a capsule or tablet, Didanosine Oral Solution may be prescribed.

**Didanosine in combination with other antiretroviral medication**

Didanosine chewable/dispersible buffered Tablets will always be taken in combination with other antiretroviral medication. Make sure to follow the instructions within the supplied package leaflet.

**If you take more Didanosine than you should**

If you take too many tablets or if someone accidentally swallows some, there is no immediate danger. However, you should contact your doctor, healthcare provider, or the nearest hospital emergency department for further advice.
If you forget to take Didanosine
Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Didanosine can cause side effects, although not everybody gets them. When treating HIV infection, it is not always possible to differentiate between unwanted effects caused by Didanosine, or those caused by any other medicines you may be taking at the same time, or by the HIV disease. For this reason, it is important that you inform your doctor or healthcare provider of any change in your health.

Short-term adverse reactions (side effects) to combination antiretroviral therapy are common. After you start taking Didanosine Tablets, headache, insomnia, nausea and vomiting, abdominal pain (cramps), diarrhea, fatigue, and malaise may occur. These reactions are usually mild and disappear within a few weeks even if treatment is continued.

Rare and very rare long-term adverse reactions include lactic acidosis, hepatic steatosis, pancreatitis, liver failure, and muscle toxicity.

Very commonly reported side effects are diarrhea, dry mouth, headache, nausea and vomiting, itching, changes in the distribution of body fat, breast enlargement, and darkening of the complexion (known as “hyperpigmentation”).

Less common but severe side effects include:
- allergic reactions (itchy skin rash, hives, difficulty breathing or tightness in the chest, wheezing, swelling of the mouth, face, lips, or tongue)
- blurred vision or other vision changes
- chest pain
- numbness, pain, or tingling in the hands, arms, legs, or feet
- confusion
- dark urine
- dizziness or fainting
- fast, slow, or irregular heartbeat
- fever or chills
- seizures
- severe muscle pain or cramping
- severe stomach pain

Call your doctor or healthcare provider immediately if you experience or think you are experiencing any of these side effects.

Combination antiretroviral therapy may cause a condition called lactic acidosis, a build-up of lactic acid in the body that can cause dehydration and coma. Lactic acidosis has been reported on rare occasions in patients taking NRTIs. Deep, rapid breathing, drowsiness, and nonspecific symptoms such as nausea, vomiting, and stomach pain, may indicate the development of lactic acidosis.
Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (“buffalo hump”). The cause and long-term health effects of these conditions are not known at this time.

Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipemia (increased fats in the blood), and resistance to insulin.

If you experience any side effects, think you are experiencing side effects, or any side effect you experience becomes serious, or if you notice any possible side effects not listed in this leaflet, tell your doctor, health care provider, or pharmacist immediately.

5. STORING DIDANOSINE CHEWABLE/DISPERSIBLE BUFFERED TABLETS, 100 mg, 150 mg, and 200 mg

Store below 30ºC (86ºF).

Do not use Didanosine chewable/dispersible buffered Tablets after the expiration (expiry) date, which is stated on the bottle or outer packaging or carton. The expiration (expiry) date refers to the last day of the month (for example, an expiry date of “October 2010” means the medicine’s expiry is October 31, 2010).

Do not use Didanosine chewable/dispersible buffered Tablets if there is any sign that the packaging has been opened or tampered with, or if you notice any visible signs of deterioration such as fading in color or discoloration of any of the tablets, or if any of the tablets are brittle or break easily.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines that are no longer required. Proper disposal of medicine will help protect the environment.

6. FURTHER INFORMATION

What Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg contain

The active ingredient of Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg is didanosine. The other ingredients are aspartame, calcium carbonate, crospovidone, magnesium hydroxide, magnesium stearate, microcrystalline cellulose, sorbitol and orange flavor (maltodextrin, natural and artificial flavors and alpha tocopherol).

What Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg look like and contents of the packaging

100 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘45’ on the other side.

150 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘46’ on the other side.

200 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘47’ on the other side.
Each strength is packaged in bottles of 60 (sixty) tablets.

For further information about this medicinal product, please contact: Aurobindo Pharma Ltd, Plot No. 2, Maitrivihar Ameerpet, Hyderabad 500 038, Andhra Pradesh, India.
SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Didanosine chewable/dispersible buffered Tablet 100 mg contains 100 mg of didanosine.
Each Didanosine chewable/dispersible buffered Tablet 150 mg contains 150 mg of didanosine.
Each Didanosine chewable/dispersible buffered Tablet 200 mg contains 200 mg of didanosine.
For a full list of excipients see 6.1

3. PHARMACEUTICAL FORM
100 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘45’ on the other side.
150 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘46’ on the other side.
200 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘47’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Didanosine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2 Posology and method of administration
Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg are for oral use.
Didanosine therapy should be prescribed by a physician experienced in the management of HIV-1 infection.
The usual dose of didanosine for adults and adolescents $\geq 60$ kg (132 lbs) is 400 mg daily, preferably taken in divided doses of 200 mg twice daily.
The usual dose of didanosine for adults, adolescents, and children weighing $\leq 60$ kg (132 lbs) is 250 mg a day taken in divided doses of 125 mg twice daily.
Patients whose management requires once-daily dosing may take the usual recommended dose in a single daily dose (400 mg daily for adults and adolescents weighing 60 kg, and 200 mg daily for adults and adolescents weighing less than 60 kg).

The usual dose of didanosine for children weighing 20-24 kg (44-53 lbs) is 200 mg once daily or 100 mg twice daily. The usual dose of didanosine for children weighing between 25-60 kg (54-132 lbs) is 250 mg once daily or 125 mg twice daily.

Children should be assessed for the ability to chew and swallow tablets. If a child is unable to reliably chew and swallow tablets, tablets may be dispersed in one ounce of water. If additional flavoring is desired, the dispersion may be diluted with one ounce of clear apple juice. Stir this diluted dispersion just prior to consumption. The dispersion with clear apple juice is stable at room temperature, 17° to 23° C (62° to 73° F), for up to one hour.

Didanosine chewable/dispersible buffered Tablets should be taken on an empty stomach at least 30 minutes before or 2 (two) hours after eating. For either once-daily or twice-daily regimens, patients must take at least two of the appropriate strength tablets at each dose to provide adequate buffering and prevent gastric acid degradation of didanosine. Because of the need for adequate buffering, the 200-mg strength tablet should only be used as a component of a once-daily regimen. To reduce the risk of gastrointestinal side effects, patients should take no more than four tablets at each dose.

**Dose Adjustments**

*Clinical and/or laboratory signs suggestive of pancreatitis:* Consider prompt dose suspension and careful evaluation. Pancreatitis is a known serious complication among HIV infected patients. It has been associated with didanosine therapy and has been fatal in some cases. Didanosine should be used only with extreme caution in patients with a history of pancreatitis. Positive relationships have been found between the risk of pancreatitis and daily dose of didanosine. Whenever warranted by clinical conditions, didanosine should be suspended until the diagnosis of pancreatitis is excluded by appropriate laboratory and imaging techniques. Similarly, when treatment with other medicinal products known to cause pancreatic toxicity is required (e.g. pentamidine), didanosine should be suspended whenever possible. If concomitant therapy is unavoidable, there should be close observation. Dose interruption should be considered when biochemical markers of pancreatitis have significantly increased, even in the absence of symptoms. Significant elevations of triglycerides are a known cause of pancreatitis and warrant close observation Didanosine should not be used in patients with confirmed pancreatitis.

*Peripheral Neuropathy:* Patients on didanosine may develop toxic peripheral neuropathy, usually characterized by bilateral symmetrical distal numbness, tingling, foot pain, and (less frequently) in the hands. Whenever warranted by clinical conditions, didanosine therapy should be suspended until resolution of symptoms. Many patients tolerate a reduced dose after resolution of symptoms. With symptoms of peripheral neuropathy may tolerate a reduced dose of didanosine after resolution of the symptoms of peripheral neuropathy after drug discontinuation. If neuropathy recurs after resuming didanosine, permanent discontinuation should be considered.

*Liver Disease:* Caution should be exercised when administering didanosine to any patient with known risk factors for liver disease. Liver failure of unknown etiology has occurred rarely in patients on didanosine. Treatment with didanosine should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity
Renal Impairment: Didanosine dosing must be modified in patients with reduced creatinine clearance and in patients receiving hemodialysis. Data from two studies indicate that the apparent oral clearance of didanosine decreased and the terminal elimination half-life increased as creatinine clearance decreased.

**Recommended Didanosine Dosage in Patients with Renal Impairment by Body Weight**

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<th>Creatinine Clearance (mL/min)</th>
<th>At least 60 kg</th>
<th>Less than 60 kg</th>
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<tr>
<td>At least 60</td>
<td>200 mg twice daily&lt;sup&gt;1&lt;/sup&gt;</td>
<td>125 mg twice daily&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>30-59</td>
<td>100 mg twice daily or 200 mg once daily</td>
<td>150 mg once daily or 75 mg twice daily</td>
</tr>
<tr>
<td>10-29</td>
<td>125 mg once daily</td>
<td>125 mg once daily</td>
</tr>
<tr>
<td>&lt;10</td>
<td>125 mg once daily</td>
<td>75 mg once daily</td>
</tr>
</tbody>
</table>

*based on studies using a buffered formulation of didanosine

<sup>1</sup> 400 mg QD in patients whose management requires once-daily dosing

<sup>2</sup> 250 mg QD in patients whose management requires once-daily dosing

4.3 Contraindications

Didanosine is contraindicated in patients with clinically significant hypersensitivity to didanosine or to any of the components contained in the formulation.

Didanosine is contraindicated in patients with confirmed pancreatitis or peripheral neuropathy.

4.4 Special warnings and special precautions for use

*Transmission of HIV*

Antiretroviral therapy has not been proven to prevent the risk of transmission of HIV to others through sexual contact or contamination with blood.

*Pancreatitis*

Fatal and nonfatal pancreatitis has occurred during therapy with didanosine used alone or in combination regimens in both treatment-naïve and treatment-experienced patients. Didanosine should be suspended in patients with signs or symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis. Patients in whom didanosine is used in combination with stavudine may be at increased risk for pancreatitis. When treatment with life-sustaining drugs known to cause pancreatic toxicity is required, suspension of didanosine therapy is recommended. In patients with risk factors for pancreatitis, didanosine should be used with extreme caution and only if clearly indicated. Patients with advanced HIV-1 infection, especially the elderly, are at increased risk of pancreatitis and should be followed closely. Patients with renal impairment may be at greater risk for pancreatitis if treated without dose adjustment.

*Liver Disease*

The safety and efficacy of didanosine has not been established in HIV-infected patients with pre-existing liver disease. During combination antiretroviral therapy, patients with preexisting liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities, including severe and potentially fatal hepatic events. If there is evidence of
worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Lactic Acidosis and/or severe hepatomegaly with steatosis
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including didanosine and other antiretrovirals. Hyperlactatemia is defined as a venous lactate level > 2 mmol/L but false positive results due to faulty collection are common. If lactate is elevated, the test should be repeated with particular attention to patient rest and hydration. Patients with elevated serum lactate levels may be asymptomatic, critically ill, or may have non-specific symptoms such as dyspnea, fatigue, nausea, diarrhea, vomiting, and abdominal pain. Lactic acid levels < 5 mmol/L may not require treatment. Symptomatic patients usually have levels > 5 mmol/L and require discontinuation of all treatment including zidovudine. Lactic acid levels > 10 mmol/L are a medical emergency carrying a high risk of death. Seriously ill patients require supportive treatment, which may include intravenous hydration, mechanical ventilation, and/or dialysis. Recovery may be protracted.

Lactic acidosis may be associated with pancreatitis, liver failure, renal failure and motor paralysis. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents.

Immune reconstitution syndrome
In HIV infected individuals with severe immunodeficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Such reactions have typically been observed within the first few weeks or months of therapy. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterium infections, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Optimal therapy has not been determined. Anti-inflammatory therapy may attenuate symptoms but many cases resolve spontaneously.

Lipodystrophy and metabolic abnormalities
Combination antiretroviral therapy may lead to abnormal redistribution of body fat including central obesity, dorsocervical fat pad enlargement, peripheral and facial subcutaneous fat wasting (lipoatrophy), and breast enlargement.

Mitochondrial dysfunction
Nucleoside and nucleotide analogues have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage. There have been reports of mitochondrial dysfunction in HIV-negative infants exposed in utero and/or post-natally to nucleoside analogues. The main adverse events reported are hematological disorders (anemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events are often transitory. Some late-onset neurological disorders have been reported (hypertonia, convulsion, abnormal behavior). Whether the neurological disorders are transient or permanent is currently unknown. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV-negative children, should have clinical and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.
4.5 Interaction with other medicinal products and other forms of interaction

Coadministration of didanosine and allopurinol results in increased systemic exposure to didanosine, which may increase didanosine-associated toxicity.

Exposure to the active metabolite of didanosine (dideoxyadenosine 5’-triphosphate) is increased when didanosine is coadministered with ribavirin. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin.

Coadministration of ganciclovir and didanosine can increase systemic levels of didanosine. Appropriate doses for this combination, in terms of safety and efficacy, have not been established.

Coadministration of methadone and didanosine can decrease systemic levels of didanosine concentration. Appropriate doses for this combination, in terms of safety and efficacy, have not been established.

Exposure to didanosine is increased when coadministered with tenofovir disoproxil fumarate. Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. A dose reduction of didanosine to 250 mg (adults weighing ≥ 60 kg with creatinine clearance ≥ 60 mL/min) or 200 mg (adults weighing < 60 kg with creatinine clearance ≥ 60 mL/min) once daily is recommended. Didanosine and tenofovir may be taken together in the fasting state. However, if tenofovir is taken with food, didanosine should be taken on an empty stomach (at least 30 minutes before food or 2 hours after food). The appropriate dose of didanosine coadministered with tenofovir in patients with creatinine clearance < 60 mL/min has not been established.

Coadministration of tenofovir disoproxil fumarate with didanosine should be undertaken with caution, and patients should be monitored closely for didanosine related toxicities and clinical response.

Use of didanosine should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop.

Suppression of CD4 cell counts has been observed in patients receiving tenofovir disoproxil fumarate with didanosine at a dose of 400 mg daily.

4.6 Pregnancy and lactation

Pregnancy

Didanosine is assigned FDA Pregnancy Category B status (“animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women”). Reproduction studies have been performed in rats and rabbits at doses up to 12 and 14.2 times the estimated human exposure (based upon plasma levels), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to didanosine.

At approximately 12 times the estimated human exposure, didanosine was slightly toxic to female rats and their pups during mid- and late lactation. These rats showed reduced food intake and body weight gains but the physical and functional development of the offspring was not impaired.
and there were no major changes in the F2 generation. A study in rats showed that didanosine and/or its metabolites are transferred to the fetus through the placenta. Animal reproduction studies are not always predictive of human response.

There are no adequate and well-controlled studies of didanosine in pregnant women. Didanosine should be used during pregnancy only if the potential benefit justifies the potential risk.

Fatal lactic acidosis has been reported in pregnant women who received the combination of didanosine and stavudine with other antiretroviral agents. It is unclear if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues.

The combination of didanosine and stavudine should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential risk. Healthcare providers caring for HIV-infected pregnant women receiving didanosine should be alert for early signs and symptoms of lactic acidosis/hepatic steatosis syndrome.

**Nursing Mothers**

It is recommended that HIV-infected mothers not breastfeed their infants to avoid risking transmission of HIV. Because of both the potential for HIV transmission and for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving didanosine.

4.7 **Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

4.8 **Undesirable effects**

Short-term adverse reactions to combination antiretroviral therapy are common. At the beginning of therapy, headache, insomnia, nausea and vomiting, abdominal pain or cramps, diarrhea, fatigue, and malaise may occur. These reactions are usually mild and disappear within a few weeks even if treatment is continued.

Common long-term adverse reactions include hyperpigmentation. Rare and very rare long-term adverse reactions include lactic acidosis, hepatic steatosis, pancreatitis, liver failure, and muscle toxicity.

The following adverse events have been reported in controlled clinical trials and case series during treatment of HIV-1 infection with didanosine. These events have been identified during post-approval use of didanosine. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are included here due to their seriousness, frequency of reporting, causal connection to didanosine, or a combination of these factors.

**General:** alopecia, anaphylactoid reaction, chills/fever, pain, and redistribution/accumulation of body fat

**Gastroenterologic Disorders:** anorexia, dyspepsia, flatulence; liver-symptomatic hyperlactatemia, lactic acidosis, and hepatic steatosis; hepatitis and liver failure.
**Exocrine Gland Disorders**: pancreatitis (including fatal cases), sialoadenitis, parotid gland enlargement, dry mouth, dry eyes

**Hematologic Disorders**: anemia, leukopenia, thrombocytopenia.

**Metabolic Disorders**: diabetes mellitus, hypoglycemia, hyperglycemia

**Musculoskeletal**: myalgia (with or without elevations in creatine kinase), rhabdomyolysis including acute renal failure and hemodialysis, athralgia, neuropathy

**Ophthalmologic**: retinal depigmentation and optic neuritis

### 4.9 Overdose

There is no known antidote for didanosine overdosage. In phase 1 studies, in which buffered formulations of didanosine were administered at doses ten times the currently recommended dose, toxicities included pancreatitis, peripheral neuropathy, diarrhea, hyperuricemia, and hepatic dysfunction. Didanosine is not dialyzable by peritoneal dialysis, although there is some clearance by hemodialysis.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiretroviral, ATC code: J05AF01

Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'-hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5’-triphosphate. Dideoxyadenosine 5’-triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5’ triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

**Clinical efficacy**

Using didanosine in a chewable/dispersible buffered tablet formulation, the effect of didanosine BID administration, alone or in combination with zidovudine, was evaluated in several major randomized, controlled clinical trials (ACTG 175, ACTG 152, DELTA, CPCRA 007). These trials confirmed the reduced risk of HIV disease progression or death with didanosine chewable/dispersible buffered tablets therapy, alone or in combination with zidovudine, as compared with zidovudine monotherapy in HIV infected individuals, including symptomatic and asymptomatic adults with CD4 counts < 500 cells/mm3 and children with evidence of immunosuppression.

The primary demonstration of clinical benefits of didanosine has been made through the ACTG 175 trial with a buffered tablet formulation of didanosine administered twice daily (BID). This study showed that eight weeks of treatment with zidovudine, didanosine chewable/dispersible tablets BID, or didanosine chewable/dispersible tablets BID plus zidovudine, decreased mean plasma HIV RNA by 0.26, 0.65 and 0.93 log10 copies/ml, respectively. In the tritherapy setting, the combination of didanosine chewable/dispersible tablets (200 mg) BID plus stavudine and indinavir has been compared to zidovudine plus lamivudine and indinavir in a randomized open
label study (START II, n= 205). Through 48 weeks of treatment, results favored the didanosine chewable/dispersible tablets arm. However, no formal conclusion can be drawn on the equivalence of the two regimens. Since didanosine exhibits a very long intracellular half-life (> 24 hours), permitting the accumulation of its pharmacologically active ddATP-moiety for extended time periods, administration of the total daily dose of didanosine chewable/dispersible buffered tablets in a once daily (QD) dosing regimen has been explored through clinical studies.

Several clinical studies have been performed with didanosine chewable/dispersible buffered tablets administered once daily, including the following:

- In the tritherapy setting, the randomized open label study-147 demonstrated that, in mostly asymptomatic patients (n= 123) that were stable on their first combination therapy containing didanosine chewable/dispersible buffered tablets BID, the shift to a similar combination therapy with didanosine chewable/dispersible buffered tablets once daily did not impact at short term (24 weeks) on the existing antiviral efficacy.

- The randomized open label study-148 (n= 756) compared didanosine chewable/dispersible buffered tablets once daily plus stavudine and nelfinavir, to zidovudine plus lamivudine and nelfinavir. After 48 weeks of treatment, results favored the zidovudine (BID) + lamivudine + nelfinavir arm compared to didanosine chewable/dispersible buffered tablets (once-daily) + stavudine + nelfinavir arm in term of proportion of patients with undetectable viral load (the proportion of patients with HIV RNA copies < 400 copies/ml was 53% for the didanosine chewable/dispersible tablets-containing arm and 62% for the comparator). However, no conclusions can be drawn on this study due to methodological issues.

Current evidence indicates that the incidence of resistance to didanosine is an infrequent event and the resistance generated is modest in degree. Didanosine-resistant isolates have been selected in vivo and are associated with specific genotype changes in the reverse transcriptase codon region (codons L74V (most prevalent), K65R, M184V and T69S/G/D/N). Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutation. Mutant viruses containing the L74V substitution show a decline in viral fitness and these mutants quickly revert to wild type in the absence of didanosine. Cross-resistance between didanosine and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is unlikely. Cross-resistance between didanosine and nucleoside reverse transcriptase inhibitors is observed in isolates containing multi-resistant mutations such as Q151M and T69SXX (an amino acid substitution with a 2-amino acid insertion) and multiple nucleoside analogue associated mutations (NAMs).

5.2 Pharmacokinetic properties

Adults

Absorption: Didanosine is rapidly degraded at an acidic pH. Therefore, the tablets contain buffering agents designed to increase gastric pH. The administration of didanosine with a meal results in a significant decrease (about 50%) in bioavailability. Didanosine chewable/dispersible buffered tablets should be administered at least 30 minutes before a meal. A study in 10 asymptomatic HIV seropositive patients demonstrated that administration of didanosine chewable/dispersible buffered tablets 30 min to 1 hour before a meal did not result in any significant changes in the bioavailability of didanosine compared to administration under fasting conditions. Administration of the tablets 1 to 2 hours after a meal was associated with a 55% decrease in Cmax and AUC values, which was comparable to the decrease observed when the formulation was given immediately after a meal. In 30 patients receiving didanosine 400 mg once
daily in the fasted state as didanosine chewable/dispersible tablets, single dose AUC was 2516 ± 847 ng.h/ml (34%) (mean ± SD [% CV]) and Cmax was 1475 ± 673 ng/ml (46%).

**Distribution:** The volume of distribution at steady state averages 54 l, suggesting that there is some uptake of didanosine by body tissues. The level of didanosine in the cerebrospinal fluid (CSF), one hour after infusion, averages 21% of that of the simultaneous plasma level.

**Biotransformation:** The metabolism of didanosine in humans has not been evaluated. Based on animal studies, it is presumed that it follows the same pathways responsible for the elimination of endogenous purines.

**Elimination:** The average elimination half-life after IV administration of didanosine is approximately 1.4 hours. Renal clearance represents 50% of total body clearance (800 ml/min), indicating that active tubular secretion, in addition to glomerular filtration, is responsible for the renal elimination of didanosine. Urinary recovery of didanosine is approximately 20% of the dose after oral treatment. There is no evidence of didanosine accumulation after the administration of oral doses for 4 weeks.

**Hepatic impairment:** No significant changes in the pharmacokinetics of didanosine were observed among hemophiliac patients with chronic, persistent elevations in liver function enzymes (n=5), which may be indicative of impaired hepatic function; hemophiliac patients with normal or less severe increases in liver function enzymes (n=8); and non-hemophiliac patients with normal enzyme levels (n=8) following a single IV or oral dose. No conclusion can be drawn regarding the metabolism of didanosine, which may be altered in patients with severe hepatic impairment (see section 4.2).

**Children**

**Absorption:** Variability in the amount of didanosine absorbed in children is greater than in adults. The absolute bioavailability of didanosine administered orally was approximately 36% after the first dose and 47% at steady state.

**Distribution:** The CSF didanosine level averages 46% of that of the simultaneous plasma level after IV administration of doses of 60 or 90 mg/m2 and equivalent oral doses of 120 or 180 mg/m2. Measurable concentrations of didanosine in the CSF were detectable for up to 3.5 hours after dosing.

**Elimination:** The average elimination half-life after IV didanosine administration is approximately 0.8 hours. Renal clearance represents approximately 59% of the total body clearance (315 ml/min/m2), indicating that both renal and non-renal pathways are involved in the elimination. Urinary recovery of didanosine is approximately 17% of dose after oral treatment. There is no evidence of didanosine accumulation after oral administration for an average of 26 days.

5.3 Preclinical safety data

The lowest didanosine dose to cause death in acute toxicity studies in the mouse, rat and dog was greater than 2000 mg/kg which is equivalent to approximately 300 times the maximum recommended human dose.

**Repeated dose toxicity:** Repeat-dose oral toxicity studies revealed evidence of a dose-limiting skeletal muscle toxicity in rodents (but not in dogs) following long-term (> 90 days) dosing with
Didanosine at doses that were approximately 1.2 - 12 times the estimated human dose. Additionally, in repeat dose studies, leukopenia was observed in dogs and rats, and gastrointestinal disturbances (soft stool, diarrhea) were seen in dogs at doses approximately 5 - 14 times the maximum human dose.

*Carcinogenicity:* In the carcinogenicity studies, non-neoplastic alterations have been observed including skeletal muscle myopathy, hepatic alterations and an exacerbation of spontaneous age-related cardiomyopathy. Lifetime dietary carcinogenicity studies were conducted in mice and rats for 22 or 24 months, respectively. No drug-related neoplasms were observed in any didanosine-treated groups of mice during, or at the end of, the dosing period. In rats, statistically significant increased incidences of granulosa cell tumours in females receiving the high dose, of subcutaneous fibrosarcomas and histiocytic sarcomas in males receiving the high dose and of haemangiomas in males receiving the high and intermediate dose of didanosine were noted. The drug-relationship and clinical relevance of these statistical findings were not clear.

*Genotoxicity:* Results from the genotoxicity studies suggest that didanosine is not mutagenic at biologically and pharmacologically relevant doses. At significantly elevated concentrations *in vitro*, the genotoxic effects of didanosine are similar in magnitude to those seen with natural DNA nucleosides.

*Reproduction:* In rats, didanosine did not impair the reproduction ability of male or female parents following treatment prior to and during mating, gestation and lactation at daily didanosine doses up to 1000 mg/kg/day. In a perinatal and postnatal reproduction study in rats, didanosine did not induce toxic effects.

6. **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Aspartame, calcium carbonate, crospovidone, magnesium hydroxide, magnesium stearate, microcrystalline cellulose, sorbitol and orange flavor (maltodextrin, natural and artificial flavors and alpha tocopherol)

6.2 **Incompatibilities**

Not applicable.

6.3 **Shelf life**

24 months

6.4 **Special precautions for storage**

Store below 30ºC (86ºF)

6.5 **Nature and contents of container**

Bottles of 60 tablets
6.6 Instructions for use and handling and disposal

No special requirements.

7. Supplier

Aurobindo Pharma Ltd, Plot No. 2, Maitrivihar Ameerpet, Hyderabad 500 038, Andhra Pradesh, India

8. DATE OF USFDA TENTATIVE APPROVAL

July 10, 2006
LABELING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Didanosine chewable/dispersible buffered Tablets 100 mg
Didanosine chewable/dispersible buffered Tablets 150 mg
Didanosine chewable/dispersible buffered Tablets 200 mg

1. NAME OF THE MEDICINAL PRODUCT

Didanosine chewable/dispersible buffered Tablets 100 mg
Didanosine chewable/dispersible buffered Tablets 150 mg
Didanosine chewable/dispersible buffered Tablets 200 mg

2. STATEMENT OF ACTIVE SUBSTANCES

Each 100 mg tablet contains 100 mg of didanosine
Each 150 mg tablet contains 150 mg of didanosine
Each 200 mg tablet contains 200 mg of didanosine

3. LIST OF EXCIPIENTS

Aspartame, calcium carbonate, crospovidone, magnesium hydroxide, magnesium stearate, microcrystalline cellulose, sorbitol and orange flavor (maltodextrin, natural and artificial flavors and alpha tocopherol)

4. PHARMACEUTICAL FORM AND CONTENTS

Chewable/dispersible buffered tablets with the following appearance:

100 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘45’ on the other side.

150 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘46’ on the other side.

200 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘47’ on the other side.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

Keep out of reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

8. EXPIRATION DATE

<EXP MM/YYYY>

9. SPECIAL STORAGE CONDITIONS

Store below 30ºC (86ºF)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF SUPPLIER

Aurobindo Pharma Ltd, Plot No. 2, Maitrivihar Ameerpet, Hyderabad 500 038, Andhra Pradesh, India

12. MANUFACTURER’S BATCH NUMBER

<Batch> <Lot> <number>

13. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

14. INSTRUCTIONS FOR USE
SCIENTIFIC DISCUSSION
**DISCUSSION**

<table>
<thead>
<tr>
<th>Name of the Finished Pharmaceutical Product</th>
<th>didanosine chewable/dispersible buffered tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplier</td>
<td>Aurobindo Pharma, Ltd.</td>
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<tr>
<td>Active Pharmaceutical Ingredient (API)</td>
<td>didanosine</td>
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<tr>
<td>International Nonproprietary Name</td>
<td>didanosine</td>
</tr>
<tr>
<td>Pharmacotherapeutic Group (ATC Code)</td>
<td>J05AF02</td>
</tr>
<tr>
<td>Therapeutic Indication</td>
<td>Didanosine chewable/dispersible buffered Tablets are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents</td>
</tr>
</tbody>
</table>
1. Introduction

Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg are indicated for the treatment of Human Immunodeficiency Virus (HIV-1) infection in combination with other antiretroviral agents.

Didanosine chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg are not indicated for use in patients with clinically significant hypersensitivity to didanosine or any of the components contained in the formulation.

It is recommended that therapy is initiated only on the advice of a physician experienced in the diagnosis and management of HIV/AIDS.

2. Assessment of Quality

Introduction
The assessment was conducted by the USFDA as an abbreviated new drug application (ANDA) reviewed under the President’s Emergency Plan for AIDS Relief (PEPFAR).

Composition
Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg present in slightly different form based on dosage strength:

100 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘45’ on the other side.

150 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘46’ on the other side.

200 mg: White to off-white, slightly mottled, round, flat-faced beveled edge tablets with debossed ‘D’ on one side and ‘47’ on the other side.

Other inactive ingredients include aspartame, calcium carbonate, crospovidone, magnesium hydroxide, magnesium stearate, microcrystalline cellulose, sorbitol and orange flavor (maltodextrin, natural and artificial flavors and alpha tocopherol).

Control of active pharmaceutical ingredient (API)
Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg controls were consistent with cGMP and USP requirements and take into account product- and process-specific needs and information.

Control testing of the finished medicinal product
The release and shelf-life specifications are consistent with requirements of major internationally used pharmacopoeias and guidelines for chewable/dispersible buffered tablets. The test methods have been adequately validated.

Stability
Updated stability data for the drug product package in the proposed marketing containers was provided.
• Three lots were tested at 3 accelerated conditions and 2 long term conditions.
• Two lots were tested at all 5 climatic conditions for 3 months in each condition, and one lot was tested in each condition (see below) for 6 months, 3 months, 3 months, 9 months, and 6 months, respectively.

Accelerated conditions: 40°C ± 2°C/ 75% RH, 50°C ± 2°C/ARH, and 25°C ± 2°C/80% RH.

Long term conditions: 30°C ± 2°C/70% RH (data for containers of 60 tablets), and 30°C ± 2°C/70% RH (data for simulated bulk packs).

All results conformed to specifications. Based on the stability data provided the proposed 2 year expiration dating period is acceptable.

3. Assessment of Bioequivalence

Aurobindo Pharma Ltd. conducted a bioequivalence study under fasting conditions comparing its product to Videx® chewable/dispersible buffered Tablets manufactured by Bristol-Myers Squibb. This study is acceptable.

The dissolution testing is also acceptable. The formulations for the 100 mg and 150 mg are proportionally similar to the 200 mg strength test product, which underwent bioequivalence testing. The waivers of in vivo bioequivalence requirements for the 100 mg and 150 mg of the test products were granted. The 100 mg and 150 mg tablets of the test product are therefore deemed bioequivalent to the 100 mg and 150 mg tablets, respectively, of the comparator product.

4. Summary of Product Safety and Efficacy

4.1 Introduction

Background
Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg have been shown to conform to the same appropriate standards of quality, efficacy and safety as those required of the innovator’s product. According to the submitted data on quality and bioavailability it is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Videx® chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg, for which benefits have been proven in terms of virological and immunological efficacy.

Product Design
The development strategy for Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg was concentrated on compatibility of the active ingredient didanosine with the excipients identified to match the dissolution profile of the innovator, thus producing a robust formulation.

Clinical Safety
The clinical safety of this product is considered to be acceptable when the guidances and restrictions presented in the Summary of Product Characteristics (SPC), Part 4 of this Public Assessment Report, are taken into consideration. See the SPC, Section 4 (“Clinical Particulars”) for discussion of contraindications, special precautions, interactions, use in pregnancy, patient exposure (including overdosage), interactions, and adverse events.
Approved Indication
Didanosine is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents.

Clinical Pharmacology

Pharmacodynamics
Nucleoside reverse transcriptase inhibitor. ATC Code: J05AF02

Didanosine (2',3'-dideoxyinosine) is an inhibitor of the in vitro replication of HIV in cultured human cells and cell lines. After didanosine enters the cell, it is enzymatically converted to dideoxyadenosine-triphosphate (ddATP), its active metabolite. In viral nucleic acid replication, incorporation of this 2',3'-dideoxynucleoside prevents chain extension, and thereby inhibits viral replication. In addition, ddATP inhibits HIV-reverse transcriptase by competing with dATP for binding to the enzyme's active site, preventing proviral DNA synthesis. The relationship between in vitro susceptibility of HIV to didanosine and clinical response to therapy has not been established. Likewise, in vitro sensitivity results vary greatly and methods to establish virologic responses have not been proven.

Pharmacokinetics
Didanosine is susceptible to degradation by stomach acid. Absorption of didanosine from the GI tract therefore varies, and is also affected by dosage form, presence of food, and gastric pH. Because of this, didanosine tablets and powder contain buffering agents. Didanosine should be given 30 minutes before or 2 (two) hours after meals, on an empty stomach. (Administration within 5 minutes of a meal reduces didanosine peak blood levels by approximately 50%.) Oral absorption is approximately 33—43% in the fasting state. The AUC of the delayed-release capsules is equivalent to buffered tablets. Didanosine chewable tablets are 20—25% more bioavailable than the powder for oral solution. Dosing recommendations for each product reflect these pharmacokinetic differences. The Tmax for didanosine increases from approximately 0.67 hours for the buffered tablets to 2 hours for the delayed-release capsules. Protein binding of didanosine is less than 5%, which contributes to its extensive distribution. CSF concentrations of didanosine reach 21-85% of plasma concentrations.

Drug Interactions, related side effects and contraindications
Coadministration of didanosine and allopurinol results in increased systemic exposure to didanosine, which may increase didanosine-associated toxicity.

Exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin.

Coadministration of ganciclovir and didanosine can increase systemic levels of didanosine. Appropriate doses for this combination, in terms of safety and efficacy, have not been established.

Coadministration of methadone and didanosine can decrease systemic levels of didanosine concentration. Appropriate doses for this combination, in terms of safety and efficacy, have not been established.
Exposure to didanosine is increased when coadministered with tenofovir disoproxil fumarate. Increased exposure may cause or worsen didanosine-related clinical toxicities, including pancreatitis, symptomatic hyperlactatemia/lactic acidosis, and peripheral neuropathy. Use of didanosine with tenofovir disoproxil fumarate should be suspended if signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop.

Refer to Section 4.5 in the Summary of Product Characteristics in this Public Assessment Report for a complete discussion of drug interactions related to didanosine use.

**Contraindications**

Didanosine is contraindicated in patients with clinically significant hypersensitivity to didanosine or to any of the components contained in the formulation, and in patients with confirmed pancreatitis or peripheral neuropathy.

**Clinical Efficacy**

Clinical efficacy of Didanosine chewable/dispersible Tablets is discussed at length in Section 5.1 (“Pharmacodynamic Properties”) in the Summary of Product Characteristics (Part 4) in this Public Assessment Report.

**Clinical Safety**

Clinical safety of Didanosine chewable/dispersible Tablets is discussed at length in Section 5.3 (“Pre-clinical Safety”) in the Summary of Product Characteristics (Part 4) in this Public Assessment Report. See the Summary of Product Characteristics, Section 4 (“Clinical Particulars”) for discussion of contraindications, special precautions, interactions, use in pregnancy, patient exposure (including overdosage), interactions, and adverse events.

5. **Overall Conclusion and benefit risk assessment**

**Quality**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics (Part 4). Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

**Bioequivalence**

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg have been shown to be bioequivalent to Videx® chewable/dispersible buffered Tablets 100 mg, 150 mg, and 200 mg.

**Clinical Efficacy and Safety**

Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg are considered effective and safe to use when the guidance and restrictions presented in the Summary of Product Characteristics (Part 4 of this Public Assessment Report) are taken into consideration.
Benefit risk assessment
Based on USFDA assessment of data on quality, bioequivalence, safety, and efficacy, the benefit risk profile of Didanosine chewable/dispersible buffered Tablets, 100 mg, 150 mg, and 200 mg, was considered acceptable for the following indication: HIV infection in combination with other antiretroviral agents.

Products added to the WHO prequalification list on the basis of USFDA tentative approval rely on scientific assessment and inspections conducted by the USFDA. A product listed as USFDA tentatively approved indicates that although existing patents and/or other marketing exclusivity prevent marketing of this product in the USA, the product meets all of USFDA’s safety, efficacy, and manufacturing quality standards required for marketing in the USA, and is eligible for purchase with PEPFAR funds.

For further information about this medicinal product, please contact:
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