LEGRAM 150 mg TABLETS
P1522196

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NOVAGEN PHARMA

SKEDULERINGSTATUS:

SUID-AFRIKA: S4

EIENDOMSNAAM EN DOSEERVORM:

LEGRAM 150 mg TABLETS (Tablet)

SAMESTELLING:

Elke filmbedekte tablet bevat lamivudien 150 mg.

FARMAKOLOGIESE KLASSIFIKASIE:

A 20.2.8 Antivirusmiddels.

FARMAKOLOGIESE WERKING:

In-vitro is lamivudien 'n selektiewe inhibeerder van MIV-1 en MIV-2 replisering, insluitende sidovudien weerstandbiedende kliniese isolate van die menslike immuuntekort virus (MIV). Lamivudien word intrasellulêr na die aktiewe 5-trifosfaat gemetaboliseer wat die RNA- en DNA-afhanklike aktiwiteite van MIV trutranskriptase inhibeer deur beëindiging van die virus DNA ketting. Lamivudien meng nie met sellulêre deoksinukleotied-metabolisme in nie en het min effek op soogdiersel- en mitochodriale DNA-inhoud. *In-vitro* toon lamivudien lae sitotoksisiteit teen perifere bloedlimfosiete, gevestigde limfosiet- en monosietmakrofaag sellyne, asook teen 'n verskeidenheid van beenmurg progenitorselle. *In-vitro* het lamivudien daarom 'n hoë terapeutiese indeks.

'n Afname in *in-vitro* sensitiwiteit teen lamivudien is vir MIV-isolate uit pasiënte wat voorheen terapie met lamivudien ontvang het, aangemeld.

Dit is aangetoon dat lamivudien bykomend tot of sinergisties met ander anti-MIV middels, veral sidovudien, in die inhibisie van replisering van MIV in selkultuur werk.

In-vitro studies toon aan dat sidovudien weerstandbiedende virusisolate sidovudiensensitief mag word wanneer hulle weerstand teen lamivudien opbou.

FARMAKOKINETIKA:

Farmakokinetika in volwassenes:

Na orale toediening word lamivudien goed geabsorbeer met 'n biobeskikbaarheid van ongeveer 80 %. Die gemiddelde tyd (T_{maks}) tot maksimum serumkonsentrasie (K_{maks}) is ongeveer 1 uur. Teen terapeutiese dosisvlakke van 4 mg/kg/dag (as twee 12-uurlikses dosisse) was K_{maks} in die orde van 1 – 1,5 µg/ml.

Die gemiddelde volume van verspreiding in intraveneuse studies is aangemeld as 1,3 l/kg en die gemiddelde terminale halfleeftyd van eliminasie is 5 tot 7 ure. Die gemiddelde sistemiese suiwering van lamivudien is ongeveer 0,32 l/kg/uur, met hoofsaaklik niersuiwering van meer as 70 % via aktiewe buissekresie, met min lewermetabolisme - minder as 10%. Die intrasellulêre halfleeftyd van lamivudien trifosfaat aktiewe metaboliet word verleng, met 'n gemiddeld van langer as 10 ure in perifere bloedlimfosiete. 'n Vertraging in T_{maks} en afname in K_{maks} is waargeneem wanneer saam met voedsel toegedien is. Geen dosisaanpassing is egter nodig nie aangesien die biobeskikbaarheid van lamivudien nie verander word nie. Lamivudien toon beperkte binding aan albumien en toon lineêre farmakokinetika oor die terapeutiese dosisrykwydte. Medetoediening van sidovudien lei tot 'n 13 % toename in sidovudien blootstelling en 'n 28 % toename in die plasmavlakke daarvan. Geen dosisaanpassing is nodig nie aangesien dit nie as betekenisvol in pasiëntveiligheid beskou word nie.

Beperkte data toon aan dat lamivudien die sentrale senuweestelsel binnedring en die serebrospinale vloeistof (SSV) bereik. Die werklike mate van penetrasie of verwantskap met enige kliniese doeltreffendheid is nie bekend nie.

Farmakokinetika in kinders:

Oor die algemeen is die farmakokinetika in pediatriese pasiënte soortgelyk aan dié in volwassenes. Die absolute biobeskikbaarheid word egter met ongeveer 65 % in pediatriese pasiënte verminder, met 'n toename in suiwering van 0,52 l/kg/uur.

Daar bestaan slegs beperkte data vir pasiënte < 3 maande oud.

INDIKASIES:

LEGRAM 150 mg TABLETS word aangedui as deel van antiretrovirus kombinasieterapie vir die behandeling van MIV-besmette volwassenes en kinders.

KONTRA-INDIKASIES:

Hipersensitiwiteit teen enige van die bestanddele.

WAARSKUWINGS:

Pasiënte wat **LEGRAM 150 mg TABLETS** en ander antiretrovirus-middels ontvang mag voortgaan om opportunistiese infeksies en ander komplikasies van MIV-besmetting op te doen.

Pasiënte behoort daarom onder noukeurige toesig van mediese praktisyns met ondervinding in die behandeling van pasiënte met MIV-geassosieerde siektes, gehou word.

Dit is nie bewys dat huidige antiretrovirusterapie, insluitende **LEGRAM 150 mg TABLETS**, die risiko van oordraging van MIV na ander persone deur seksuele kontak of bloedkontaminasie voorkom nie.

Melksuurasidose en erge hepatomegalie met steatose, insluitende fatale gevalle, is met die gebruik van lamivudien alleen of in kombinasie, in die behandeling van MIV-infeksie aangemeld.

INTERAKSIES:

Die plasmavlakke van sidovudien word nie beduidend verander wanneer dit saammet **LEGRAM 150 mg TABLETS** toegedien word nie (sien **"FARMAKOKINETIKA"**).

Teen terapeutiese dosisse veroorsaak trimetopriem, 'n bestanddeel van ko-trimoksasool, 'n toename van 40 % in die plasmakonsentrasies van lamivudien. Dit vereis geen dosisaanpassing nie, tensy die pasiënt ook aan belemmerde nierfunksie ly.

Die toediening van ko-trimoksasool saammet die **LEGRAM 150 mg TABLETS**/sidovudien kombinasie in pasiënte met belemmerde nierfunksie behoort noukeurig geëvalueer te word.

LEGRAM 150 mg TABLETS mag die intrasellulêre fosforilasie van salsitabien inhibeer wanneer hierdie twee medisinale produkte gelyktydig gebruik word. Dit word daarom aanbeveel dat **LEGRAM 150 mg TABLETS** nie in kombinasie met salsitabien gebruik word nie.

SWANGERSKAP EN LAKTASIE:

Veiligheid in swangerskap en laktasie is nie vasgestel nie.

DOSIS EN GEBRUIKSAANWYSINGS:

Volwassenes en adolessente ouer as 12 jaar:

Die aanbevole dosis van **LEGRAM 150 mg TABLETS** is 300 mg per dag. Dit mag as 300 mg een keer of 150 mg twee keer per dag toegedien word.

Die voubiljet van sidovudien moet geraadpleeg word vir die dosis en toediening daarvan.

Vir pasiënte wat minder as 50 kg weeg, is die aanbevole dosis van **LEGRAM 150 mg TABLETS** 2 mg/kg twee keer per dag.

Kinders ≥ 3 maande tot 12 jaar oud:

Die aanbevole dosis is 4 mg/kg twee keer per dag tot 'n maksimum van 300 mg per dag.

Kinders < 3 maande oud:

Die data is te beperk om 'n spesifieke dosis aan te beveel (sien **"FARMAKOKINETIKA"**).

LEGRAM 150 mg TABLETS kan met of sonder voedsel geneem word.

Belemmerde nier- en lewerfunksie:

Belemmerde nierfunksie, siekte-of ouderdomsverwant, beïnvloed die eliminasie van lamivudien. Verwys na die tabel hieronder vir aanbevole dosisregimes in pasiënte met 'n kreatiniensuiwering van minder as 50 ml/min.

Kreatiniensuiwering (ml /min)	Aanbevole dosis van LEGRAM 150 mg TABLETS
≥ 50	150 mg twee keer per dag
30 – 49	150 mg een keer per dag
15 – 29	150 mg eerste dosis, daarna 100 mg een keer per dag
5 – 14	150 mg eerste dosis, daarna 50 mg een keer per dag
< 5	50 mg eerste dosis, daarna 25 mg een keer per dag

Kinders > 3 maande tot 12 jaar:

Kreatiniensuiwering (ml /min)	Aanbevole dosis van LEGRAM 150 mg TABLETS
≥ 50	4 mg/kg eerste dosis, daarna 4 mg/kg twee keer per dag
30 – 49	4 mg/kg eerste dosis, daarna 4 mg/kg een keer per dag
15 – 29	4 mg/kg eerste dosis, daarna 2,6 mg/kg een keer per dag
5 – 14	4 mg/kg eerste dosis, daarna 1,3 mg/kg een keer per dag
< 5	1,3 mg/kg eerste dosis, daarna 0,7 mg/kg een keer per dag

NEWE-EFFEKTE EN SPESIALE VOORSORGSMAATREËLS:

Newe-effekte:
Die volgende newe-effekte is gedurende terapie met **LEGRAM 150 mg TABLETS** alleen, en in kombinasie met ander antiretrovirusmiddels in MIV-siekte aangemeld:

Gastroïntestinale afwykings:
Pankreatitis, boonste buikpyn, naarheid, braking en diarree is aangemeld.

Afwykings van die bloed- en limfatiese sisteem:
Neutropenie, trombositopenie en anemie het voorgekom.

Afwykings van die vel en apendiks:
Alopesie is aangemeld.

Afwykings van die sentrale en perifere senuweestelsel:
Perifere neuropatie, parestesie en hoofpyn is aangemeld.

Afwykings van die muskuloskeletale stelsel:
Artralgie, spierafwykings, insluitende minder dikwels rabdomiolise, is aangemeld.

Liggaam as geheel:
Malaise, moegheid en koors het voorgekom.

Hipersensitiwiteitsreaksies:
Veluitslag.

Veranderinge in laboratorium toetsparameters:
Verbygaande toenames in lewerensiemwaardes in serum (ALT, AST) en toenames in serumamilase is aangemeld.

Spesiale voorsorgsmaatreëls:

LEGRAM 150 mg TABLETS behoort met sorg in pasiënte met gevorderde sirrotiese lewersiekte weens chroniese hepatitis B gebruik te word, aangesien daar 'n klein risiko van terugkerende hepatitis na behandeling bestaan.

Pankreatitis:

Pankreatitis is in sommige pasiënte wat **LEGRAM 150 mg TABLETS** ontvang, waargeneem. Dit is egter onduidelik of dit weens **LEGRAM 150 mg TABLETS** of weens die onderliggende MIV-siekte is. Pankreatitis moet oorweeg word wanneer 'n pasiënt buikpyn, naarheid, braking of 'n toename in biochemiese merkers ondervind. Staak die gebruik van **LEGRAM 150 mg TABLETS** totdat 'n diagnose van pankreatitis uitgeskakel is.

Melksuurasidose / erge hepatomegalie met steatose:

Die langtermyn gebruik van **LEGRAM 150 mg TABLETS** kan tot potensieel fatale melksuurasidose lei. Simptomatiese hiperlaktasemie en melksuurasidose kom selde voor. Die kliniese eienskappe is nie-spesifiek en sluit naarheid, braking, buikpyn, dispnee, moegheid en massaverlies in. Verdagte biochemiese eienskappe sluit effens verhoogde transaminases, verhoogde laktaatdehidrogenase (LDH) en / of kreatienkinase in.

In pasiënte met verdagte simptome of biochemie moet die veneuse laktaatvlak (normaal < 2 mmol/l) gemeet word en moet as volg opgetree word:

- Laktaat 2 – 5 mmol/l: monitor gereeld en wees bedag op kliniese tekens.
- Laktaat 5 – 10 mmol/l sonder simptome: monitor noukeurig.
- Laktaat 5 – 10 mmol/l met simptome: Staak alle terapie. Sluit ander oorsake uit (bv. sepsis, uremie, diabetiese keto-asidose, tirotoksikose, limfoom).
- Laktaat > 10 mmol/l: Staak alle terapie (80% mortaliteit in gevallestudies).

'n Diagnose van melksuurasidose word bevestig deur metaboliese asidose met 'n toename in die anioongaping en 'n verhoogde laktaatvlak. Terapie behoort gestaak te word in enige asidotiese pasiënt met 'n verhoogde laktaatvlak.
Bloed vir laktaatbepalings behoort gehepariniseer en op ys gehou te word.
Na herstel behoort NTTI's vermy te word. Raadpleeg 'n spesialis oor die keuse van medikasie.
Die bogenoemde laktaatwaardes mag nie van toepassing in pediatriese pasiënte wees nie.
Melksuurasidose en erge hepatomegalie met steatose, insluitende fatale gevalle, is met die gebruik van **LEGRAM 150 mg TABLETS** alleen of in kombinasie, in die behandeling van MIV-infeksie aangemeld. Die meeste gevalle was vroue.

Sorg behoort aan die dag gelê te word wanneer **LEGRAM 150 mg TABLETS** aan pasiënte met bekende risikofaktore vir lewersiekte toegedien word (sien **"WAARSKUWINGS"**).

Die behandeling met **LEGRAM 150 mg TABLETS** behoort opgeskort te word in enige pasiënt wat kliniese tekens van melksuurasidose of hepatotoksisiteit toon, of laboratoriumbevindings het wat daarop dui.

Opportunistiese infeksies:

Opportunistiese infeksies en ander komplikasies mag aanhou om te ontwikkel in pasiënte wat **LEGRAM 150 mg TABLETS** ontvang en pasiënte behoort daarom onder sorgvuldige toesig gehou te word deur dokters met ondervinding in die behandeling van geassosieerde MIV-infeksie (sien **"WAARSKUWINGS"**).

Die risiko van MIV-oordraging na ander persone:

Pasiënte behoort daarvan bewus gemaak word dat dit nie bewys is dat huidige antiretrovirusterapie, insluitende **LEGRAM 150 mg TABLETS**, die risiko van oordraging van MIV na ander persone deur seksuele kontak of bloedoortapping voorkom nie. Daarom behoort hulle met die toepaslike voorkoming voort te gaan.

Pasiënte met matig tot erg belemmerde nierfunksie:

In pasiënte met matig tot erg belemmerde nierfunksie, is daar weens 'n afname in suiwering, 'n toename in die terminale halfleeftyd van lamivudien. Die dosis behoort daarom aangepas te word (sien **"DOSIS EN GEBRUIKSAANWYSINGS"**).

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VAN DIE BEHANDELING DAARVAN:

Die behandeling is simptomaties en ondersteunend.

IDENTIFIKASIE:

Wit tot effe-wit, filmbedekte, ovaalvormige tablette met '52' en 'Y' aan beide kante van die breeklyn aan die een kant en skoon met 'n breeklyn aan die ander kant

AANBIEDING:

1. 60 Tablette word in wit ronde 70 ml HDPE houers met 'n skroeftipe polipropileen dop met 'n induksie seëlprop verpak.
2. 60 Tablette word in wit ronde 40 ml HDPE houers met 'n kinderweerstandbiedend polipropileen dop met 'n induksie seëlprop verpak.

BERGINGSINSTRUKSIES:

Bewaar by of benede 30°C in die oorspronklike verpakking. Beskerm teen vogtigheid.

HOU BUITE BEREIK VAN KINDERS

REGISTRASIENOMMER:

SUID-AFRIKA: A40/20.2.8/0376

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE:

Novagen Pharma (Pty) Ltd
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DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET:
11 Augustus 2006

SCHEDULING STATUS:

SOUTH AFRICA: S4

PROPRIETARY NAME AND DOSAGE FORM:
LEGRAM 150 mg TABLETS (Tablet)

COMPOSITION:
Each film-coated tablet contains lamivudine 150 mg.

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION:

Lamivudine is a selective inhibitor of HIV-1 and HIV-2 replication *in-vitro,* including zidovudine-resistant clinical isolates of the human immunodeficiency virus (HIV). Lamivudine is metabolised intracellularly to the active 5-triphosphate which inhibits the RNA- and DNA-dependent activities of HIV reverse transcriptase by termination of the viral DNA chain. Lamivudine does not interfere with cellular deoxynucleotide metabolism and has little effect on mammalian cell and mitochondrial DNA content. *In-vitro,* lamivudine demonstrates low cytotoxicity to peripheral blood lymphocytes, to established lymphocyte and monocyte-macrophage cell lines, and to a variety of bone marrow progenitor cells. *In-vitro,* lamivudine therefore has a high therapeutic index.

Reduced *in-vitro* sensitivity to lamivudine has been reported for HIV isolated from patients who have received lamivudine therapy before.

Lamivudine has been shown to act additively or synergistically with other anti-HIV agents, particularly zidovudine, inhibiting the replication of HIV in cell culture.

In-vitro studies indicate that zidovudine-resistant virus isolates can become zidovudine-sensitive when they acquire resistance to lamivudine.

PHARMACOKINETICS:

Pharmacokinetics in adults:

Following oral administration, lamivudine is well absorbed with bioavailability of approximately 80 **%.** The mean time (T_{max}**)** to maximum serum concentration **(**C_{max}) is about an hour. At therapeutic dose levels of 4 mg/kg/day (as
two 12-hourly doses), C_{max} is in the order of 1-1,5 µg/ml.
The mean volume of distribution from intravenous studies has been reported as 1,3 l/kg and the mean terminal half-life of elimination as 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 l/kg/h, with predominantly renal clearance of more than 70 % via active tubular secretion, but little hepatic metabolism, at less than 10 **%.** The intracellular half-life of the lamivudine triphosphate active metabolite is prolonged, averaging over 10 hours in peripheral blood lymphocytes. A delay in T_{max} and reduction in C_{max} have been observed when co-administered with food, but no dose adjustment is needed, as lamivudine bioavailability is not altered. Lamivudine displays limited binding to albumin and exhibits linear pharmacokinetics over the therapeutic dose range. Co-administration of zidovudine results in a 13 % increase in zidovudine exposure and a 28 % increase in peak plasma levels. No dosage adjustments are necessary, as this is not considered to be of significance to patient safety. Limited data shows lamivudine penetrates the central nervous system and reaches the cerebrospinal fluid (CSF). The true extent of penetration or relationship with any clinical efficacy is unknown.

Pharmacokinetics in children:

In general, lamivudine pharmacokinetics in paediatric patients are similar to adults. However, absolute bioavailability is reduced to approximately 65 **%** in paediatric patients, with an increased clearance of 0,52 l/kg/hr.
There are limited pharmacokinetic data for patients < 3 months of age.

INDICATIONS:
LEGRAM 150 mg TABLETS is indicated as part of antiretroviral combination therapy for the treatment of HIV infected adults and children.

CONTRA-INDICATIONS:
Hypersensitivity to any of the ingredients.

WARNINGS:

Patients receiving **LEGRAM 150 mg TABLETS** and other antiretroviral agent may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.

Current antiretroviral therapy, including **LEGRAM 150 mg TABLETS**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination, in the treatment of HIV infection.

INTERACTIONS:

Zidovudine plasma levels are not significantly altered when co-administered with **LEGRAM 150 mg TABLETS, (**see **"PHARMACOKINETICS").**
An interaction with trimethoprim, a constituent of co-trimoxazole, causes a 40 % increase in lamivudine plasma concentrations at therapeutic doses. This does not require dose adjustment unless the patient also has renal impairment.
Administration of co-trimoxazole with the **LEGRAM 150 mg TABLETS**/zidovudine combination in patients with renal impairment should be carefully assessed.
LEGRAM 150 mg TABLETS may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. **LEGRAM 150 mg TABLETS** is therefore, not recommended to be used in combination with zalcitabine.

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Adults and adolescents more than 12 years of age:

The recommended dose of **LEGRAM 150 mg TABLETS** is 300 mg daily. This may be administered as either 300 mg once daily or 150 mg twice daily.

The package insert for zidovudine must be consulted for information on its dosage and administration. For patients with low body weights (less than 50 kg), the recommended oral dose of **LEGRAM 150 mg TABLETS** is 2 mg/kg twice daily.

Children ≥ 3 months to 12 years of age:
The recommended dose is 4 mg/kg twice daily up to a maximum of 300 mg daily.

Children < 3 months of age:
There is a limited data to propose specific dosage recommendations (see **"PHARMACOKINETICS"**).

LEGRAM 150 mg TABLETS can be taken with or without food.

Renal and Hepatic Impairment:
Renal impairment, whether disease- or age-related, affects lamivudine elimination. For recommended dosage regimens in patients with a creatinine clearance below 50 ml/min see table below:
Adults and adolescents >12 years of age:

Creatinine Clearance (ml/min)	Recommended dose of LEGRAM 150 mg TABLETS
≥ 50	150 mg twice daily
30 - 49	150 mg once daily
15 - 29	150 mg first dose, then 100 mg once daily
5 - 14	150 mg first dose, then 50 mg once daily
< 5	50 mg first dose, then 25 mg once daily

Children > 3 months to 12 years:

Creatinine Clearance (ml/min)	Recommended dose of LEGRAM 150 mg TABLETS
≥ 50	4 mg/kg first dose, then 4 mg/kg twice daily
30 - 49	4 mg/kg first dose, then 4 mg/kg once daily
15 - 29	4 mg/kg first dose, then 2,6 mg/kg once daily
5 - 14	4 mg/kg first dose, then 1,3 mg/kg once daily
< 5	1,3 mg/kg first dose, then 0,7 mg/kg once daily

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

The following side-effects have been reported during therapy of HIV disease with **LEGRAM 150 mg TABLETS** alone, and in combination with other anti-retrovirals.

Gastro-intestinal disorders:
Pancreatitis, upper abdominal pain, nausea, vomiting and diarrhoea have been reported.

Blood and lymphatic system disorders:
Neutropenia, thrombocytopenia and anaemia have occurred.

Skin and appendages disorders:
Alopecia has been reported.

Central and Peripheral Nervous system disorders:
Peripheral neuropathy, paraesthesia and headache have been reported.

Musculoskeletal system disorders:
Arthralgia, muscle disorders including less frequently, rhabdomyolysis have been reported.

Body as a whole:
Malaise, fatigue and fever have occurred.

Hypersensitivity reactions:
Skin rash.

Changes in laboratory test parameters:
Transient rises in serum liver enzymes (AST, ALT) and rises in serum amylase have been reported**.**

Special precautions:
LEGRAM 150 mg TABLETS should be used with caution in patients with advanced cirrhotic liver disease due to chronic Hepatitis B infection, as there is a small risk of rebound hepatitis post treatment.

Pancreatitis:
Pancreatitis has been observed in some patients receiving **LEGRAM 150 mg TABLETS**. However it is unclear whether this is due to **LEGRAM 150 mg TABLETS** or to underlying HIV disease. Pancreatitis must be considered whenever a patient develops abdominal pain, nausea, vomiting or elevated biochemical markers. Discontinue use of **LEGRAM 150 mg TABLETS** until diagnosis of pancreatitis is excluded.

Lactic acidosis/severe hepatomegaly with steatosis:
Long-term use of **LEGRAM 150 mg TABLETS** can result in potentially fatal lactic acidosis. Symptomatic hyperlactacaemia and lactic acidosis are uncommon. Clinical features are non-specific, and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase.
In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/l), and respond as follows:
- Lactate 2 — 5 mmol/l: monitor regularly, and be alert for clinical signs.
- Lactate 5 — 10 mmol/l without symptoms: monitor closely.
- Lactate 5 — 10 mmol/l with symptoms: STOP all therapy. Exclude other causes, (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate> 10 mmol/l: STOP all therapy (80 % mortality in case studies.)

Diagnosis of lactic acidosis is confirmed by demonstrating metabolic acidosis with an increased anion gap and raised lactate level. Therapy should be stopped in any acidotic patient with a raised lactate level.
Blood for lactate assays should be heparinised and stored on ice.
After recovery, NRTI's should be avoided. Seek expert advice on medicine selection. **The above lactate values may not be applicable to paediatric patients.**

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of **LEGRAM 150 mg TABLETS** alone or in combination, in the treatment of HIV infection. Most cases were women.

Caution should be exercised when administering **LEGRAM 150 mg TABLETS** to patients with known risk factors for liver disease (see **"WARNINGS"**).
Treatment with **LEGRAM 150 mg TABLETS** should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

Opportunistic infections:

Patients receiving **LEGRAM 150 mg TABLETS** may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by medical practitioners experienced in the treatment of patients with associated HIV disease (see **"WARNINGS"**).

The risk of HIV transmission to others:

Patients should be advised that current antiretroviral therapy, including **LEGRAM 150 mg TABLETS**, has not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Patients with moderate to severe renal impairment:

In patients with moderate to severe renal impairment, the terminal half-life of lamivudine is increased due to decreased clearance. The dose should therefore be adjusted (see **"DOSAGE AND DIRECTIONS FOR USE"**).

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT:
Treatment is symptomatic and supportive.

IDENTIFICATION:
White to off white, film-coated, oval shaped tablets, debossed with '52' and 'Y' on either side of the scoreline on one side and plain with a scoreline on the other side.

PRESENTATION:
1. 60 tablets are packed in white round 70 ml HDPE containers with screw type polypropylene closure with induction sealing wad.
2. 60 tablets are packed in white round 40 ml HDPE containers with child resistant polypropylene closure with induction sealing wad.

STORAGE INSTRUCTIONS:
Store at or below 30 °C in the original package. Protect from moisture.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
SOUTH AFRICA: A40/20.2.8/0376

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
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