

PRODUCT INFORMATION

LANVIS

COMPOSITION: Thioguanine 40 mg.

ACTIONS:

Thioguanine, a derivative of mercaptopurine, is an antagonist to purine metabolism, but its precise mechanism of antineoplastic activity has not been determined. Its tumour inhibitory effects may be due to incorporation into DNA and RNA; feedback inhibition of *de novo* purine synthesis; inhibition of purine nucleotide interconversion.

INDICATIONS:

Acute myeloblastic leukaemia. Less commonly, chronic granulocytic (myelocytic, myeloid, myelogenous) leukaemia. Although superior results are generally obtained with busulphan (Myleran) in the treatment of chronic granulocytic leukaemia. LANVIS may be useful during blast crises or periods of thrombocytopenia induced by busulphan or other therapy. A degree of cross resistance exists between LANVIS (thioguanine) and Puri-Nethol (mercaptopurine) and generally it is not to be expected that patients who no longer respond to mercaptopurine will respond to thioguanine or vice versa. Unlike mercaptopurine the detoxification of LANVIS is not dependent on xanthine oxidase, hence therapy with LANVIS is not affected by the xanthine oxidase inhibitor, allopurinol (Zyloprim).

Recent evidence suggests that LANVIS is particularly useful in concurrent or sequelist combination with other antineoplastic drugs, e.g., cytosine arabinoside. Not effective for the treatment of chronic lymphocytic leukaemia or solid tumours. The aim of therapy is to achieve normal appearance of the bone marrow and peripheral blood. It is recognised, however, that in treating acute leukaemia, one may not always be able to achieve complete remissions and must be satisfied with partial improvement.

CONTRAINDICATIONS:

Hypersensitivity to any component of the preparation.

Although success may be obtained after six or more induction courses, therapy should be reviewed if remission is not achieved after two or three attempts at induction. It should not be used during viraemic states, marrow aplasia, severe anaemia, leucopenia or in bleeding states, severe liver dysfunction, renal failure or intolerance to the drug. Some of these conditions may be corrected by appropriate therapy and this allows for therapy to proceed.

PRECAUTIONS:

LANVIS IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Hepatic Effects

LANVIS IS NOT RECOMMENDED FOR MAINTENANCE THERAPY OR SIMILAR LONG TERM CONTINUOUS TREATMENTS DUE TO THE HIGH RISK OF LIVER TOXICITY ASSOCIATED WITH VASCULAR ENDOTHELIAL DAMAGE (see DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS). This liver toxicity has been observed in a high proportion of children receiving LANVIS as part of maintenance therapy for acute lymphoblastic leukaemia and in other conditions associated with continuous use of LANVIS. This liver toxicity is particularly prevalent in males. Liver toxicity usually presents as the clinical syndrome of hepatic veno-occlusive disease (hyperbilirubinaemia, tender hepatomegaly, weight gain due to fluid retention and ascites) or with signs of portal hypertension (splenomegaly, thrombocytopenia and oesophageal varices). Histopathological features associated with this toxicity include hepatoportal sclerosis, nodular regenerative hyperplasia, peliosis hepatis and periportal fibrosis.

LANVIS therapy should be discontinued in patients with evidence of liver toxicity as reversal of signs and symptoms of liver toxicity have been reported upon withdrawal.

Haematological Effects

Treatment with LANVIS causes bone marrow suppression leading to leucopenia and thrombocytopenia (see Hepatic Effects). Anaemia has been reported less frequently.

Bone marrow suppression is readily reversible if LANVIS is withdrawn early enough.

Monitoring

Patients must be carefully monitored during therapy including blood cell counts and weekly liver function tests. Early indications of liver toxicity are signs associated with portal hypertension such as thrombocytopenia out of proportion with neutropenia and splenomegaly. Elevations of liver enzymes have also been reported in association with liver toxicity but do not always occur.

DURING REMISSION INDUCTION, FULL BLOOD COUNTS MUST BE CARRIED OUT FREQUENTLY.

It may be advisable to perform liver function tests more frequently in patients with known pre-existing liver disease or in patients who are receiving thioguanine and other hepatotoxic drugs.

It is advisable to start with smaller doses in patients with liver disease, since most of the ingested drug is metabolised in the liver. The same considerations apply to renal disease because of the primarily renal excretion of the metabolites. Frequent blood counts should be undertaken during therapy, and caution must be exercised to avoid toxicity, the chief manifestation of which is depression of the bone marrow, resulting in leucopenia and eventually thrombocytopenia and bleeding.

Since the drug may have a delayed and prolonged action, it is important to withdraw the medication temporarily at the first sign of abnormally large fall in the white blood cell count or of abnormal depression of the bone marrow. Blood counts should be made at least once weekly during maintenance therapy and daily during remission induction. Supportive therapy may be

required, e.g., barrier nursing, antibiotics, antiemetics, glucocorticoids for capillary fragility, platelets and blood transfusions as appropriate.

Patients on myelosuppressive chemotherapy are particularly susceptible to a variety of infections.

During remission induction, particularly when rapid cell lysis is occurring, adequate precautions should be taken to avoid hyperuricaemia and/or hyperuricosuria and the risk of uric acid nephropathy.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of LANVIS and prone to developing rapid bone marrow depression following the initiation of treatment with LANVIS. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Some laboratories offer testing for TPMT deficiency, although these tests have not been shown to identify all patients at risk of severe toxicity. Therefore close monitoring of blood counts is still necessary.

Lesch-Nyhan syndrome:-

Since the enzyme hypoxanthine guanine phosphoribosyl transferase is responsible for the conversion of LANVIS to its active metabolite, it is possible that patients deficient in this enzyme, such as those suffering from Lesch-Nyhan syndrome, may be resistant to the drug. Resistance to azathioprine (IMURAN), which has one of the same active metabolites as LANVIS, has been demonstrated in two children with Lesch-Nyhan syndrome.

Interactions with other drugs:

The combination of busulphan and LANVIS has resulted in the development of nodular regenerative hyperplasia, portal hypertension and oesophageal varices.

The concomitant use of allopurinol to inhibit uric acid formation does not necessitate reduction of dosage of LANVIS.

As there is in vitro evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme, they should be administered with caution to patients receiving concurrent LANVIS therapy (see PRECAUTIONS).

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (See PRECAUTIONS).

Carcinogenicity, mutagenicity and impairment of fertility:

In view of its action on DNA, LANVIS is potentially mutagenic and carcinogenic

Use in Pregnancy (Category D)

LANVIS is a potent teratogen in animals, and its exhibition in pregnancy has been associated with fetal chromosome abnormality. The benefits and risks must therefore be weighed before use in pregnancy. Whenever possible, use of the drug should be deferred until after the first trimester of pregnancy.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving LANVIS.

There have been isolated cases where men who have received combinations of cytotoxic agents including LANVIS, have fathered children with congenital abnormalities.

Lactation:-

There are no reports documenting the presence of LANVIS or its metabolites in maternal milk. It is suggested that mothers receiving LANVIS should not breast feed.

ADVERSE REACTIONS:

The following convention has been utilised for the classification of frequency of undesirable effects:- Very common $\geq 1/10$ ($\geq 10\%$), Common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$), Uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$), Rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$), Very rare $< 1/10,000$ ($< 0.01\%$).

Blood and lymphatic system disorders

Very Common: Bone marrow suppression (see PRECAUTIONS)

Gastrointestinal disorders

Common: stomatitis
gastrointestinal intolerance including nausea and vomiting (requiring treatment or withholding of the drug) and diarrhoea

Rare: intestinal necrosis and perforation

Hepato-biliary disorders

Very Common: Liver toxicity associated with vascular endothelial damage when LANVIS is used in maintenance or similar long term continuous therapy which is not recommended (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

This usually presents as the clinical syndrome of hepatic veno-occlusive disease (hyperbilirubinaemia, tender hepatomegaly, weight gain due to fluid retention and ascites) or signs and symptoms of portal hypertension (splenomegaly, thrombocytopenia and oesophageal varices). Elevation of liver transaminases, alkaline phosphatase and gamma glutamyl transferase and jaundice may also occur. Histopathological features associated with this toxicity include hepatportal sclerosis, nodular regenerative hyperplasia, peliosis hepatis and periportal fibrosis.

Common: Liver toxicity during short term cyclical therapy presenting as veno-occlusive disease.

Reversal of signs and symptoms of this liver toxicity has been reported upon withdrawal of short term or long term continuous therapy.

Rare: Centrilobular hepatic necrosis has been reported in a few cases including patients receiving combination chemotherapy, oral contraceptives, high dose LANVIS and alcohol.

Other adverse reactions that have been reported include transient treatment related megaloblastic marrow changes, development of immunosuppressive states and

agranulocytosis (with consequent liability to infection requiring adequate barrier nursing and appropriate antibiotics), and thrombocytopenia requiring haemostatic measures.

DOSAGE AND ADMINISTRATION:

The dosage and duration of administration of LANVIS must be carefully adjusted for each patient to obtain optimum benefit without toxic effects. Therapy should be initiated in a specialised unit with full facilities for supportive therapy. LANVIS is usually administered in accordance with a protocol, in combination with other drugs. The following comments are for general guidance. The usual initial dose is approximately 2 to 2.5 mg/kg bodyweight/day, orally. It is usually calculated to the nearest multiple of 20 mg. The total daily dose may be given at one time. Some regimens, however, demand 12 hourly dosage.

Although the effect usually occurs slowly over a period of two to four weeks, there may occasionally be a rapid fall in leucocyte count within one or two weeks. This may occur in some adults with acute leukaemia and high total leucocyte counts, as well as certain adults with chronic granulocytic leukaemia. For this reason it is important to observe such patients closely. Daily blood counts are necessary during intensive therapy with multi-drug protocols.

LANVIS is not recommended for use during maintenance therapy or similar long term continuous treatments due to the high risk of liver toxicity (see PRECAUTIONS and ADVERSE REACTIONS).

LANVIS may be continued in the usual dosage when allopurinol is used concomitantly to inhibit uric acid formation. Smaller doses may be advisable in patients with impaired renal or hepatic function.

OVERDOSE

Signs:-

The principal toxic effect is on the bone marrow and haematological toxicity is likely to be more profound with chronic overdosage than with a single ingestion of LANVIS.

Treatment:-

As there is no known antidote the blood picture should be closely monitored and general supportive measures, together with appropriate blood transfusion instituted if necessary.

PRESENTATION:

Tablets 40 mg (cream, scored, marked WELLCOME U3B): 25's.

Each tablet contains thioguanine 40 mg as the active ingredient plus the inactive ingredients: lactose, starch-potato, acacia, magnesium stearate and stearic acid.

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