1 PRODUCT NAME

ALLMERCAP 20mg/mL oral suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ALLMERCAP oral suspension contains 20 mg/mL mercaptopurine monohydrate.

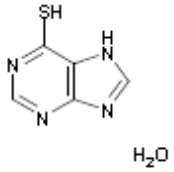
The chemical name of mercaptopurine monohydrate is 1,7-dihydro-6H-purine-6-thione hydrate.

Relative molecular mass: 170.2

Molecular formula is $C_5H_4N_4S \cdot H_2O$

CAS No.: 6112-76-1 (monohydrate)

Chemical structure is:



Mercaptopurine is odourless or practically odourless, yellow crystalline powder, with a solubility of 0.26 mg/mL in water at 37°C.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

ALLMERCAP is a pink/brown oral liquid suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ALLMERCAP oral suspension is indicated for:
Treatment of Acute Lymphoblastic Leukaemia (ALL) in paediatric patients.

4.2 Dose and method of administration

ALLMERCAP is only indicated for use in children. For children the usual dose is 2.5 mg/kg bodyweight/day, but the dose and duration of administration depend on the nature and dosage of other cytotoxic agents given in conjunction with mercaptopurine. The dosage should be carefully adjusted to suit the individual patient.

Mercaptopurine has been used in various combination therapy schedules for acute leukaemia and the literature should be consulted for details.

When allopurinol and mercaptopurine are administered concomitantly it is essential that only a quarter of the usual dose of mercaptopurine is given since allopurinol decreases the rate of catabolism of mercaptopurine.

Mercaptopurine is metabolised by the polymorphic Thiopurine Methyl Transferase (TPMT) enzyme. Patients with little or no inherited TPMT activity are at increased risk for severe toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction. TPMT

genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. TPMT testing cannot substitute for haematological monitoring in patients receiving mercaptopurine. The optimal starting dose for homozygous deficient patients has not been established (see Section 4.4 Special warnings and precautions for use).

Method of administration
ALLMERCAP may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken at the same time as milk or dairy products (see section 4.5). ALLMERCAP should be taken at least 1 hour before or 2 hours after milk or dairy products.

Renal or hepatic impairment
Consideration should be given to reducing the dosage in patients with impaired hepatic or renal function.

Patients with NUDT15 variant
Patients with inherited mutated NUDT15 gene are at increased risk for severe mercaptopurine toxicity, (see 4.4). These patients generally require dose reduction; particularly those being NUDT15 variant homozygotes (see 4.4). Genotypic testing of NUDT15 variants may be considered before initiating mercaptopurine therapy. In any case, close monitoring of blood counts is necessary.

4.3 Contraindications

- Hypersensitivity to any component of the preparation.
- Concomitant use with yellow fever vaccine (see section 4.5 Interactions with other medicines and other forms of interactions).

In view of the seriousness of the indications there are no other absolute contraindications.

4.4 Special warnings and precautions for use

Precautions

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

Co-administration of ribavirin and mercaptopurine is not advised. Ribavirin may reduce efficacy and increase toxicity of mercaptopurine (see section 4.5).

The handling of ALLMERCAP oral suspension should follow standard guidelines for the handling and disposal of cytotoxic drugs.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving ALLMERCAP oral suspension.

Immunosuppression
Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended in patients with leukaemia. In all cases, patients in remission should not receive live organism vaccines until at least 3 months after their chemotherapy treatment has been completed.

Cytotoxic and haematological monitoring
Since mercaptopurine is strongly myelosuppressive, full blood counts must be monitored daily during remission induction. Patients must be carefully monitored during therapy.

Treatment with mercaptopurine causes bone marrow suppression leading to leucopenia and

thrombocytopenia, and less frequently anaemia. Full blood counts must be taken daily during remission induction. During maintenance therapy, complete blood counts, including platelets should be performed weekly or more frequently if high dosage is used or if severe renal and or hepatic disorder is present. The mercaptopurine oral suspension and tablet are not bioequivalent with respect to peak plasma concentration, and therefore intensified haematological monitoring of the patient is advised on switching formulations.

The leucocyte and platelet counts continue to fall after treatment is stopped, so at the first sign of abnormally large fall in the counts, treatment should be interrupted immediately.

Bone marrow suppression is reversible if mercaptopurine is withdrawn early enough.

During remission induction in acute myelogenous leukaemia the patient may frequently have to survive a period of relative bone marrow aplasia and it is important that adequate supportive facilities are available.

The dosage of mercaptopurine may need to be reduced when this agent is combined with other drugs whose primary or secondary toxicity is myelosuppression (see section 4.5 Interaction with other medicines and other forms of interactions -Effect of concomitant drugs on mercaptopurine - myelosuppressive agents).

Hepatotoxicity
Mercaptopurine is hepatotoxic and liver function tests should be monitored weekly during treatment. More frequent monitoring may be advisable in those with pre-existing liver disease or receiving other potentially hepatotoxic therapy. The patient should be instructed to discontinue mercaptopurine immediately if jaundice becomes apparent.

Tumour lysis syndrome
During remission induction when rapid cell lysis is occurring, uric acid levels in blood and urine should be monitored as hyperuricaemia and/or hyperuricosuria may develop, with the risk of uric acid nephropathy.

Renal and/or hepatic impairment
Caution is advised during the administration of mercaptopurine in patients with renal impairment and/or hepatic impairment. Consideration should be given to reducing the dosage in these patients and haematological response should be carefully monitored (see section 4.2 Dose and method of administration).

TPMT testing
There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of mercaptopurine and prone to developing rapid bone marrow depression following the initiation of treatment with mercaptopurine. There have been fatal cases of myelosuppression in patients with low or absent TPMT activity treated with thiopurines. This problem could be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulphasalazine. Also a possible association between decreased TPMT activity and secondary leukaemias and myelodysplasia has been reported in individuals receiving mercaptopurine in combination with other cytotoxics (see section 4.8 Undesirable effects).

Patients should be tested for TPMT activity before starting mercaptopurine. TPMT testing cannot substitute for complete blood count monitoring in patients receiving mercaptopurine. TPMT genotyping can be used to identify patients with absent or reduced TPMT activity. Patients with low

or absent TPMT activity (homozygous for non-functional alleles) are at an increased risk of developing severe, life-threatening myelotoxicity from mercaptopurine if conventional doses are given. Alternative therapies may be considered for patients who have low or absent TPMT activity. Mercaptopurine should be administered with caution to patients having one non-functional allele (heterozygous) who are at risk for reduced TPMT activity that may lead to toxicity if conventional doses are given. Dosage reduction is recommended in patients with reduced TPMT activity.

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.

Cross resistance usually exists between mercaptopurine and tioguanine (Lanvis).

Hypersensitivity

Patients suspected to have previously presented with a hypersensitivity reaction to mercaptopurine monohydrates should not be advised to use its pro-drug azathioprine, unless the patient has been confirmed as hypersensitive to mercaptopurine monohydrate with allergological tests, and has tested negative for azathioprine. As azathioprine is a pro-drug of mercaptopurine monohydrate, patients with a previous history of hypersensitivity to azathioprine must be assessed for hypersensitivity to mercaptopurine monohydrate prior to initiating treatment.

Carcinogenesis & mutagenesis

Mercaptopurine in common with other anti-metabolites is potentially mutagenic and chromosome damage has been reported in rats and humans

Increases in chromosomal aberrations were observed in the peripheral lymphocytes of leukaemic patients and in a hypernephroma patient who received an unstated dose of mercaptopurine and in patients with chronic renal disease treated at doses of 0.4-1.0 mg/kg/day.

In view of its action on cellular deoxyribonucleic acid (DNA), mercaptopurine is potentially carcinogenic and consideration should be given to the theoretical risk of carcinogenesis with this treatment. Three cases have been documented of the occurrence of acute nonlymphatic leukaemia in patients who received mercaptopurine for non-neoplastic disorders. A single case has been reported where a patient was treated for pyoderma gangrenosum with mercaptopurine monohydrate and later developed acute nonlymphatic leukaemia.

A patient with Hodgkin's disease treated with mercaptopurine and multiple additional cytotoxic agents developed acute myelogenous leukaemia.

Twelve and a half years after mercaptopurine treatment for myasthenia gravis, a female patient developed chronic myeloid leukaemia.

Reports of hepatosplenic T-cell lymphoma in the inflammatory bowel disease population (this is an unregistered indication) have been received when azathioprine (the prodrug to mercaptopurine) or mercaptopurine is used either with or without concomitant treatment with anti-TNF alpha antibody. This rare type of T cell lymphoma has an aggressive disease course and is usually fatal (see section 4.8 Undesirable effects).

Carcinogenicity

Patients receiving immunosuppressive therapy, including mercaptopurine, are at an increased risk of

developing lymphoproliferative disorders and other malignancies, notably skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ. The increased risk appears to be related to the degree and duration of immunosuppression. It has been reported that discontinuation of immunosuppression may provide partial regression of the lymphoproliferative disorder.

A treatment regimen containing multiple immunosuppressants (including thiopurines) should therefore be used with caution as this could lead to lymphoproliferative disorders, some with reported fatalities. A combination of multiple immunosuppressants, given concomitantly increases the risk of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders.

Macrophage activation syndrome
ALLMERCAP is only indicated for treatment of ALL in paediatric patients.

Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with autoimmune conditions, in particular with inflammatory bowel disease (IBD) (unlicensed indication), and there could potentially be an increased susceptibility for developing the condition with the use of mercaptopurine. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible, and treatment with mercaptopurine should be discontinued. Physicians should be attentive to symptoms of infection such as EBV and cytomegalovirus (CMV), as these are known triggers for MAS.

Infections
Patients treated with mercaptopurine alone or in combination with other immunosuppressive agents, including corticosteroids, have shown increased susceptibility to viral, fungal and bacterial infections, including severe or atypical infection, and viral reactivation. The infectious disease and complications may be more severe in these patients than in non-treated patients.

Prior exposure to or infection with varicella zoster virus should be taken into consideration prior to starting treatment. Local guidelines may be considered, including prophylactic therapy if necessary. Serologic testing prior to starting treatment should be considered with respect to hepatitis B. Local guidelines may be considered, including prophylactic therapy for cases which have been confirmed positive by serologic testing. Cases of neutropenic sepsis have been reported in patients receiving mercaptopurine for ALL.

Lesch-Nyhan Syndrome

Limited evidence suggests that neither mercaptopurine monohydrate nor its pro-drug azathioprine are effective in patients with hypoxanthine-guanine-phosphoribosyltransferase deficiency (Lesch–Nyhan syndrome). The use of mercaptopurine monohydrate or azathioprine is not recommended in these patients.

UV Exposure

Patients treated with mercaptopurine monohydrate are more sensitive to the sun. Exposure to sunlight and UV light should be limited, and patients should be advised to wear protective clothing and to use a sunscreen with a high protection factor.

Patients with NUDT15 variant
Patients with inherited mutated NUDT15 gene are at increased risk for severe mercaptopurine toxicity, such as early leukopenia and alopecia, from conventional doses of thiopurine therapy. They generally require dose reduction, particularly those being NUDT15 variant homozygotes (see section

4.2 Dose and method of administration). The frequency of NUDT15 c.415C>T has an ethnic variability of approximately 10 % in East Asians, 4 % in Hispanics, 0.2 % in Europeans and 0 % in Africans. Patients of Asian ethnicity are particularly at risk, due to the increased frequency of the mutation in this population. The optimal starting dose for heterozygous or homozygous deficient patients has not been established. Genotypic and phenotypic testing of NUDT15 variants should be considered before initiating thiopurine therapy in all patients (including paediatric patients) to reduce the risk of thiopurine-related severe leukocytopenia and alopecia, especially in Asian populations. In any case, close monitoring of blood counts is necessary.

Metabolic and nutritional disorders
Purine analogues (azathioprine and mercaptopurine) may interfere with the niacin pathway, potentially leading to nicotinic acid deficiency (pellagra). Cases of pellagra have been reported with the use of purine analogues, particularly in patients with chronic inflammatory bowel disease. The diagnosis of pellagra should be considered in patients with a localised pigmented rash (dermatitis), gastroenteritis, or neurological deficits including cognitive deterioration. Appropriate medical care with niacin/nicotinamide supplementation must be initiated and dose reduction or discontinuation of purine analogues must be considered.

Hypoglycaemia
Cases of symptomatic hypoglycaemia have been reported in children with ALL receiving mercaptopurine (see section 4.8 Undesirable effects). The majority of reported cases were in children under the age of six or with a low body mass index.

Cholestasis of Pregnancy
Cholestasis of pregnancy has occasionally been reported in association with mercaptopurine therapy (see section 4.6 Fertility, pregnancy, and lactation). Monitoring of 6-methyl mercaptopurine (6-MMP) should be considered in the presence of pruritus with elevated maternal total serum bile acid levels in second trimester of pregnancy to establish early diagnosis and minimise impact on the foetus. If cholestasis of pregnancy occurs, case by case assessment is necessary considering the risk-benefit profile of the product (potential withdrawal/dose reduction).

Excipients
This medicinal product contains aspartame (E951), a source of phenylalanine. May be harmful for people with phenylketonuria. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

It also contains sodium methyl parahydroxybenzoate and sodium ethyl parahydroxybenzoate which may cause allergic reaction (possibly delayed).

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Long term use increase the risk of dental caries and it is essential that adequate dental hygiene is maintained.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of yellow fever vaccine is contraindicated, due to the risk of fatal disease in immunocompromised patients. Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.3 Contraindications, section 4.4 Special warnings and precautions for use).

Effect of concomitant drugs on mercaptopurine

Ribavirin

Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of a pro-drug of mercaptopurine and ribavirin; therefore concomitant administration of ribavirin and mercaptopurine is not advised (see section 4.4).

Myelosuppressive agents

When mercaptopurine is combined with other myelosuppressive agents, caution should be used; dose reductions may be needed based on haematological monitoring (see section 4.4).

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors

Xanthine oxidase activity is inhibited by allopurinol, oxipurinol and thiopurinol, which results in reduced conversion of biologically active 6-thioinosinic acid to biologically inactive 6-thiouric acid.

When allopurinol, oxipurinol and/or thiopurinol and mercaptopurine are administered concomitantly it is essential that only a 25% of the usual dose of mercaptopurine is given (see section 4.2 Dose and method of administration) since allopurinol decreases the rate of catabolism of mercaptopurine.

Other xanthine oxidase inhibitors, such as febuxostat, may decrease the metabolism of mercaptopurine monohydrate. Concomitant administration is not recommended as data are insufficient to determine an adequate dose reduction.

Aminosalicylates

There is in vitro and in vivo evidence that aminosalicylate derivatives (e.g. olsalazine, mesalazine or sulphasalazine) inhibit the TPMT enzyme. Therefore, lower doses of mercaptopurine may need to be considered when administered concomitantly with aminosalicylate derivatives (see PRECAUTIONS).

Following unregulated consumption of salicylates, sulphonamides or undefined tranquillisers by patients receiving mercaptopurine therapy, a slower onset of pancytopenia has been documented.

Methotrexate

Methotrexate may increase mercaptopurine monohydrate exposure (area under curve, AUC). Methotrexate (20 mg/m^2 orally) increased mercaptopurine AUC by approximately 31% and methotrexate (2 or 5 g/m^2 intravenously) increased mercaptopurine AUC by 69% and 93%, respectively. When administered concomitantly with high dose methotrexate, the mercaptopurine dose may need adjustment to maintain a suitable white blood cell count.

Infliximab

Interactions have been observed between azathioprine, a pro-drug of mercaptopurine monohydrate, and infliximab. Patients receiving ongoing azathioprine experienced transient increases in 6-TGN (6-thioguanine nucleotide, an active metabolite of azathioprine) levels and decreases in the mean leukocyte count in the initial weeks following infliximab infusion, which returned to previous levels after 3 months. Therefore, close monitoring of haematological parameters is necessary if mercaptopurine is administered with concomitant infliximab therapy.

Effect of mercaptopurine on other drugs

Anticoagulants

Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with mercaptopurine; therefore higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with mercaptopurine.

Anti-epileptic medicines

Cytotoxic agents may decrease the intestinal absorption of phenytoin. Careful monitoring of the phenytoin serum levels is recommended. It is possible that the levels of other anti-epileptic medicinal products may also be altered. Serum antiepileptic levels should be closely monitored during treatment with mercaptopurine monohydrate, making dose adjustments as necessary.

Other forms of interaction

The administration of mercaptopurine with food may decrease systemic exposure slightly but this is unlikely to be of clinical significance. Therefore, ALLMERCAP may be taken with food or on an empty stomach, but patients should standardise the method of administration. The dose should not be taken with milk or dairy products since they contain xanthine oxidase, an enzyme which metabolises mercaptopurine and might therefore lead to reduced plasma concentrations of mercaptopurine.

4.6 Fertility, pregnancy and lactationUse In Pregnancy

Pregnancy Category D

Cytotoxic agents can produce spontaneous abortion, fetal loss and birth defects. Both sexually active males and females should use effective methods of contraception during treatment and for at least three months for males and six months for females after receiving the last dose.

Substantial transplacental and transamniotic transmission of mercaptopurine and its metabolites from the mother to the foetus have been shown to occur.

The use of mercaptopurine monohydrate should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving ALLMERCAP oral suspension.

Mercaptopurine has been shown to be embryotoxic in rats at doses that are not toxic to the mother. It has also been proven to be embryolethal when administered at higher doses in the first half of the gestation period. The potential risk for humans is largely unknown.

Maternal exposure

Normal offspring have been born after mercaptopurine therapy administered as a single chemotherapy agent during human pregnancy, particularly when given prior to conception or after the first trimester.

Abortions and prematurity have been reported after maternal exposure. Multiple congenital abnormalities have been reported following maternal mercaptopurine treatment in combination with other chemotherapy agents.

Cholestasis of pregnancy has occasionally been reported in association with azathioprine (a prodrug of mercaptopurine) therapy. Early diagnosis and discontinuation of mercaptopurine may minimise impact on the foetus. A careful assessment of benefit to the mother and impact on the foetus should be performed, if cholestasis of pregnancy is confirmed (see section 4.4 Special warnings and precautions for use).

Paternal exposure

Congenital abnormalities and spontaneous abortions have been reported after paternal exposure to mercaptopurine.

A leukaemia patient treated with mercaptopurine 100 mg/day (plus splenic irradiation) throughout pregnancy gave birth to a normal, premature baby. A second baby, born to the same mother who was treated as before, together with busulfan 4 mg/day, had multiple severe abnormalities, including corneal opacities, microphthalmia, cleft palate and hypoplasia of the thyroid and ovaries. The use of mercaptopurine should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

Transient profound oligospermia was observed in a young man who received mercaptopurine 150 mg/day plus prednisone 80 mg/day for acute leukaemia. Two years after cessation of the chemotherapy he had a normal sperm count and fathered a normal child.

Use in Lactation
Mercaptopurine has been detected in the breast milk of renal transplant patients receiving immunosuppressive therapy with azathioprine, a pro-drug of mercaptopurine and thus mothers receiving mercaptopurine should not breast feed.

4.7 Effects on ability to drive and use machines
No studies on the effect on the ability to drive and use machines have been performed. A detrimental effect on these activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

Adverse Effects
The following convention has been utilised for the classification of undesirable effects: *very common* (≥1/10), *common* (≥1/100 and <1/10), *uncommon* (≥1/1000 and <1/100), *rare* (≥1/10,000 and <1/1000), *very rare* (<1/10,000).

Infections and infestations
Uncommon: bacterial and viral infections, infections associated with neutropenia.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Rare: neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ.
Very rare: secondary leukaemia and myelodysplasia
Frequency not known: hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease (an unlicensed indication) when used in combination with or without concomitant anti-TNF alpha antibody has been reported (see section 4.4 Special warnings and precautions for use).

Blood and lymphatic system disorders
Very common: bone marrow suppression; leucopenia and thrombocytopenia. The main side effect of treatment with mercaptopurine is bone marrow suppression leading to leucopenia and thrombocytopenia.
Common: anaemia

Immune system disorders
Hypersensitivity reactions with the following manifestations have been reported.

Uncommon: arthralgia; skin rash; drug fever
Rare: facial oedema

Metabolism and nutrition disorders
Common: anorexia
Frequency not known: hypoglycaemia, pellagra (see section 4.4)

Gastrointestinal disorders
Common: nausea; vomiting; pancreatitis in the IBD population (an unlicensed indication); stomatitis and diarrhoea
Uncommon: pancreatitis (in the licensed indication); oral ulceration
Rare: intestinal ulceration
Not known: cheilitis

Hepatobiliary disorders
Common: biliary stasis; hepatotoxicity
Uncommon: hepatic necrosis
Frequency not known: Portal hypertension*, nodular regenerative hyperplasia*, sinusoidal obstruction syndrome*, cholestasis of pregnancy

*In patients with inflammatory bowel disease (IBD), and unlicensed indication.

Mercaptopurine is hepatotoxic in animals and humans. The histological findings in humans have shown hepatic necrosis and biliary stasis.
The incidence of hepatotoxicity varies considerably and can occur with any dose, but more frequently when the recommended dose of 2.5 mg/kg bodyweight daily is exceeded.
Monitoring of liver function tests may allow early detection of liver toxicity. This is usually reversible if mercaptopurine therapy is stopped soon enough. However, irreversible liver damage leading to a fatal outcome has occurred.

Skin and subcutaneous tissue disorders
Rare: alopecia
Frequency not known: photosensitivity reaction, erythema nodosum

Reproductive system and breast disorders
Rare: transient oligospermia.

General disorders and administration site conditions
Frequency not known: Mucosal inflammation

Investigations
Frequency not known: Coagulation factors decreased

4.9 Overdose

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Contact the Poisons Information Centre on telephone 0800 764 766 for advice on management of overdose.

Symptoms

Gastro-intestinal effects, including nausea, vomiting, diarrhoea and anorexia may be early symptoms of overdosage having occurred. 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 mercaptopurine.

The risk of overdosage is also increased when allopurinol is being given concomitantly with mercaptopurine. Liver dysfunction and gastroenteritis may also occur.

Treatment
As there is no known antidote, blood counts should be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary. Active measures (such as the use of activated charcoal) may not be effective in the event of mercaptopurine overdose unless the procedure can be undertaken within 60 minutes of ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Mercaptopurine is an analogue of adenine, one of the bases required for nucleic acid biosynthesis, and of the purine base hypoxanthine. Hence mercaptopurine acts as an antimetabolite and interferes with the synthesis of nucleic acids in proliferating cells. Its metabolites are also pharmacologically active.

5.2 Pharmacokinetic properties
Absorption of an oral tablet dose of mercaptopurine is incomplete and variable averaging about 50% of the administered dose. The half-life of mercaptopurine in the circulation is of the order of 90 minutes. It is extensively metabolised and excreted via the kidneys and the active metabolites have a longer half-life than the parent drug. Mercaptopurine has pKa's of 7.7 and 11.

In a study of healthy adult volunteers given a single dose of ALLMERCAP oral suspension, the mean Cmax was found to be 86.6 ng/mL at 45 minutes. The mean AUC0-t was found to be 121.6 ng/mL.h.

Comparison of the oral tablet and oral suspension shows the AUC to be 14% (90%CI 8, 21) and Cmax to be 39% (90%CI 22, 58) higher with the oral suspension.

5.3 Preclinical safety data
Mercaptopurine in common with other anti-metabolites is potentially mutagenic and chromosome damage has been reported in rats and humans.

Mercaptopurine causes embryolethality and severe teratogenic effects in mice, rats, hamsters and rabbits at doses that are non-toxic to the mother. In all species, the degree of embryotoxicity and type of malformations is dependent on the dose and the stage of gestation at the time of administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
ALLMERCAP oral suspension also contains the following inactive ingredients: xanthan gum, aspartame, rubus idaeus (raspberry juice), sodium methyl hydroxybenzoate, sodium ethyl hydroxybenzoate, potassium sorbate, sodium hydroxide, and purified water.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

18 months.

56 days after first opening.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

ALLMERCAP is a pink/brown oral liquid suspension in a 100 mL amber glass bottle with a tamper evident child resistant closure. The product is supplied with a bottle adaptor and 2 oral syringes (graduated to 1 mL and 5 mL).

6.6 Special precautions for disposal <and other handling>

Safe handling

Anyone handling Allmercap should wash their hands before and after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling Allmercap.

Allmercap contact with skin or mucous membrane must be avoided. If Allmercap comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water. Spillages must be wiped immediately.

Women who are pregnant, planning to be or breast-feeding should not handle Allmercap.

Parents / care givers and patients should be advised to keep Allmercap out of the reach and sight of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Keep the bottle tightly closed to protect the integrity of the product and minimise the risk of accidental spillage.

The bottle should be shaken vigorously for at least 30 seconds to ensure the oral suspension is well mixed.

Disposal

Allmercap is cytotoxic. Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic drugs.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Link Pharmaceuticals Ltd.
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139 Quay Street
Auckland 1010
NEW ZEALAND
Tel: +64 9 358 7146

9 DATE OF FIRST APPROVAL

18 November 2016

10 DATE OF REVISION OF THE TEXT

22 September 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of safety information related to live organism vaccines, cytotoxic and haematological monitoring, TPMT testing, NUDT15, metabolic and nutritional disorders, cholestasis of pregnancy.
4.5	Addition of information related to infliximab
4.6	Addition of safety information related to use in pregnancy, cholestasis of pregnancy
4.8	Addition of adverse event cholestasis of pregnancy