

AUSTRALIAN PRODUCT INFORMATION – ZYLOPRIM (ALLOPURINOL) TABLETS

1 NAME OF THE MEDICINE

Allopurinol.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYLOPRIM tablets contain 100 mg or 300 mg allopurinol.

Excipients with known effect: lactose monohydrate. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ZYLOPRIM 100 mg tablets are white, biconvex round tablets, one side embossed with 'AP' and '100' separated by a break line and plain on the other side.

ZYLOPRIM 300 mg tablets are white, biconvex round tablets, one side embossed with 'AP' and '300' separated by a break line and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Main clinical manifestations of urate/uric acid deposition. These are gouty arthritis, skin tophi and/or renal involvement through crystal deposition or stone formation. Such clinical manifestations may occur in: idiopathic gout; uric acid lithiasis; acute uric acid nephropathy; neoplastic disease and myeloproliferative disease with high cell turnover rates, in which high urate levels occur either spontaneously or after cytotoxic therapy, certain enzyme disorders which lead to overproduction of urate and involve:

- hypoxanthine guanine phosphoribosyltransferase including Lesch-Nyhan syndrome,
- glucose 6-phosphatase including glycogen storage disease,
- phosphoribosylpyrophosphate synthetase,
- phosphoribosylpyrophosphate amidotransferase.

ZYLOPRIM is indicated for the management of 2,8-dihydroxyadenine (2,8-DHA) renal stones related to deficient activity of adenine phosphoribosyl transferase.

ZYLOPRIM is indicated for the management of recurrent mixed calcium oxalate renal stones in the presence of hyperuricosuria, when fluid, dietary and similar measures have failed.

4.2 DOSE AND METHOD OF ADMINISTRATION

The dosage should be adjusted by monitoring serum urate concentrations and urinary urate/uric acid levels at appropriate intervals.

Dose frequency

ZYLOPRIM may be taken orally once a day after a meal. It is well tolerated, especially after food. Should the daily dosage exceed 300 mg and gastrointestinal intolerance be manifested, a divided dose regimen may be appropriate.

Adults

2 to 10 mg/kg bodyweight/day or 100 to 200 mg daily in mild conditions; 300 to 600 mg daily in moderately severe conditions; 700 to 900 mg daily in severe conditions.

Children under 15 years

10 to 20 mg/kg bodyweight/day or 100 to 400 mg daily. Use in children is rarely indicated, except in malignant conditions (especially leukaemia) and certain enzyme disorders such as Lesch-Nyhan syndrome.

Use in the Elderly

In the absence of specific data, the lowest dosage which produces satisfactory urate reduction should be used. Particular attention should be paid to the dosage advice in renal disorder and Precautions.

Renal impairment

Since allopurinol and its metabolites are excreted by the kidney, impaired renal function may lead to retention of the drug and/or its metabolites with consequent prolongation of plasma half-lives. In the presence of impaired renal function, serious consideration should be given to initiating treatment with a maximum dose of 100 mg/day and increasing it only if the serum and/or urinary urate response is unsatisfactory. In severe renal insufficiency, it may be advisable to use less than 100 mg/day or to use single doses of 100 mg at longer intervals than one day. Alternative schedules based on creatinine clearances are unsatisfactory because of the imprecision of low clearance values.

If facilities are available to monitor plasma oxipurinol concentrations, the dose should be adjusted to maintain plasma oxipurinol levels below 100 µmol/L (15.2 µg/mL).

Renal dialysis

Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required two to three times a week, consideration should be given to an alternative dosage schedule of ZYLOPRIM 300 to 400 mg immediately after each dialysis with none in the interim.

Dosage in hepatic impairment

Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.

Treatment of high urate turnover conditions

(eg. neoplasia, Lesch-Nyhan syndrome)

It is advisable to correct existing hyperuricaemia and/or hyperuricosuria with ZYLOPRIM before starting cytotoxic therapy. It is important to ensure adequate hydration to maintain optimum diuresis and to attempt alkalinisation of urine to increase solubility of urinary urate/uric acid. Dosage of ZYLOPRIM should be in the lower range.

If urate nephropathy or other pathology has compromised renal function, the advice given in Renal impairment (above) should be followed.

These steps may reduce the risk of xanthine and/or oxipurinol deposition complicating the clinical situation (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS)).

4.3 CONTRAINDICATIONS

ZYLOPRIM should not be administered to individuals known to be hypersensitive to allopurinol or to any other components of the formulation (see Section 6.1 LIST OF EXCIPIENTS).

ZYLOPRIM should not be given concomitantly with iron salts to patients with idiopathic haemochromatosis, nor should it be given to the immediate relatives of such patients.

Warnings

ZYLOPRIM should be withdrawn immediately when a skin rash or other evidence of sensitivity occurs.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in these patients.

Asymptomatic hyperuricaemia *per se* is **not** an indication for the use of ZYLOPRIM. Fluid and dietary modifications with management of the underlying cause may correct the condition. If other clinical conditions suggest a need for ZYLOPRIM it must be introduced at low dosage (50 to 100 mg/day) to reduce the risk of adverse reactions, and increased only if the serum urate response is unsatisfactory. Extra caution should be exercised if renal function is poor (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

ZYLOPRIM must be withdrawn immediately and permanently at the first signs of intolerance.

Dermatological Effects

ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR OTHER SIGNS WHICH MAY INDICATE AN ALLERGIC REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme exudativum), drug rash with eosinophilia and systemic symptoms (DRESS), Lyell's disease, generalised vasculitis, irreversible hepatotoxicity, and on rare occasions death. DRESS is also referred to as drug-induced hypersensitivity syndrome (DIHS) and Lyell's disease is also referred to as toxic epidermal necrolysis.

Hepatic Effects

A few cases of reversible clinical hepatotoxicity have been noted in patients taking ZYLOPRIM, and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss, or pruritus develop in patients on ZYLOPRIM, evaluation of liver function should be part of their diagnostic workup. In patients with pre-existing liver disease, periodic liver function tests are recommended during the early stages of therapy.

Hypersensitivity Effects

The occurrence of hypersensitivity reactions to ZYLOPRIM may be increased in patients with decreased renal function receiving thiazides and ZYLOPRIM concurrently. For this reason, in this clinical setting, such combinations should be administered with caution and patients should be observed closely.

Acute gouty attacks

Allopurinol treatment should not be started until an acute attack of gout has completely subsided, as further attacks may be precipitated.

In the early stages of treatment with ZYLOPRIM, as with uricosuric agents, an acute attack of gouty arthritis may be precipitated. Therefore it is advisable to give prophylaxis with a suitable anti-inflammatory agent or colchicine (0.5 mg three times a day) for at least one month.

Xanthine deposition

In conditions where the rate of urate formation is greatly increased (eg. malignant disease and its treatment, Lesch-Nyhan syndrome) the absolute concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract. This risk may be minimised by adequate hydration to achieve optimal urine dilution.

Impaction of uric acid renal stones

Adequate therapy with ZYLOPRIM will lead to dissolution of large uric acid renal pelvic stones, with the remote possibility of impaction in the ureter.

Renal Effects

Some patients with pre-existing renal disease or poor urate clearance have shown a rise in serum urea during administration of allopurinol. Although the mechanism responsible for this has not been established, patients with impaired renal function should be carefully observed during the early stages of allopurinol administration and dosage decreased or the drug withdrawn if increased abnormalities in renal function appear and persist. Patients under treatment for hypertension or cardiac insufficiency, for example with diuretics or ACE inhibitors, may have some concomitant impairment of renal function and allopurinol should be used with care in these patients.

Renal failure in association with administration of allopurinol has been observed among patients with hyperuricemia secondary to neoplastic diseases. Concurrent conditions such as multiple myeloma and congestive myocardial disease were present among those patients whose renal dysfunction increased after allopurinol was begun. Renal failure is also frequently associated with gouty nephropathy and rarely with hypersensitivity reactions associated with allopurinol. Albuminuria has been observed among patients who developed clinical gout following chronic glomerulonephritis and chronic pyelonephritis.

Haematological Effects

Bone marrow depression has been reported in patients receiving allopurinol, most of whom received concomitant drugs with the potential for causing this reaction. This has occurred as early as six weeks to as long as six years after the initiation of therapy of allopurinol. Rarely a patient may develop varying degrees of bone marrow depression, affecting one or more cell lines, while receiving allopurinol alone.

Haemochromatosis

Allopurinol's primary action in treating gout is to inhibit the enzyme, xanthine oxidase. Xanthine oxidase may be involved in the reduction and clearance of hepatically stored iron. Some rodent studies have found increased iron storage in animals treated with allopurinol, whilst others have not. A study in 28 healthy volunteers found no change in hepatic iron storage with allopurinol treatment. There are no human studies which have investigated the safety of administering allopurinol to patients with haemochromatosis. Administration of allopurinol to patients with abnormal iron storage, including haemochromatosis, should be undertaken with caution.

Use in hepatic impairment

Reduced doses should be used in patients with hepatic impairment.

Use in renal impairment

A dose reduction will be required in patients with renal impairment (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION)

Use in the elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

6-Mercaptopurine and azathioprine

When 6-mercaptopurine or azathioprine is given concurrently with ZYLOPRIM, only one-quarter of the usual dose of 6-mercaptopurine or azathioprine should be given because inhibition of xanthine oxidase will prolong their activity.

Adenine arabinoside

Evidence suggests that the plasma half-life of adenine arabinoside is increased in the presence of allopurinol. When the two products are used concomitantly extra vigilance is necessary, to recognise enhanced toxic effects.

Salicylates and uricosuric agents

Oxipurinol, the major metabolite of allopurinol and itself therapeutically active, is excreted by the kidney in a similar way to urate. Hence, drugs with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxipurinol. This may decrease the therapeutic activity of ZYLOPRIM, but the significance needs to be assessed in each case.

Chlorpropamide

If ALLOSIG is given concomitantly with chlorpropamide when renal function is poor, there may be an increased risk of prolonged hypoglycaemic activity.

Coumarin anticoagulants

There is no evidence that interaction between allopurinol and the coumarins seen under experimental conditions has any clinical significance. However, all patients receiving anticoagulants must be carefully monitored.

Phenytoin

Allopurinol may inhibit hepatic oxidation of phenytoin but the clinical significance has not been demonstrated.

Theophylline

Experimental studies of the effect of allopurinol on theophylline metabolism have produced contradictory findings. Inhibition of the metabolism of theophylline has been reported. Theophylline levels should be monitored in patients starting or increasing allopurinol therapy.

Ampicillin/Amoxicillin

An increase in the frequency of skin rash has been reported among patients receiving ampicillin or amoxicillin concurrently with allopurinol compared to patients who are not receiving both drugs. The cause of the reported association has not been established, however, it is recommended that in patients receiving allopurinol an alternative to ampicillin or amoxicillin is used where available.

Cyclosporin

Reports suggest that the plasma concentration of cyclosporin may be increased during concomitant treatment with allopurinol. The possibility of enhanced cyclosporin toxicity should be considered if the drugs are co-administered.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Reproduction studies in rabbits and rats using dosages up to 20 times the usual human dosage have not revealed any evidence of impaired fertility. Only rarely has infertility in human males and impotence occurred during allopurinol therapy, however a casual relationship to the drug has not been established.

Use in pregnancy – Pregnancy Category B2

There is inadequate evidence of safety of ALLOSIG in human pregnancy, although it has been in wide use for many years without apparent ill consequence.

One study in mice receiving a high intraperitoneal dose on days 10 to 13 of pregnancy resulted in foetal abnormalities but extensive studies of high oral doses in mice, rats and rabbits during days 8 to 16 produced none.

Use in pregnancy only when there is no safe alternative and when the disease itself carries risks for the mother or child.

Use in lactation.

Reports indicate that allopurinol and oxipurinol are excreted in human breast milk. Concentrations of 1.5 mg/L allopurinol and 53.7 mg/L oxipurinol have been demonstrated in breast milk from a woman taking allopurinol 300 mg/day. There are, however, no data concerning the effects of allopurinol, or its metabolism, on the breast-fed child.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Since adverse reactions such as somnolence, vertigo and ataxia have been reported in patients receiving allopurinol, patients should exercise caution before driving, using machinery or participating in dangerous activities where alertness is mandatory until they are reasonably certain that allopurinol does not adversely affect performance.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions are usually reversed by the reduction of dosage or complete withdrawal of ZYLOPRIM. Taking ZYLOPRIM after meals may minimise gastrointestinal disturbances. Where hypersensitivity reactions occur, allopurinol should be withdrawn immediately. Corticosteroids may be beneficial in overcoming such reactions.

Adverse reactions in association with ZYLOPRIM are rare in the overall treated population and mostly of a minor nature. The incidence is higher in the presence of renal and/or hepatic disorder.

Dermatological

These are the most common reactions and may occur at any time during treatment. They may be pruritic, maculopapular, sometimes scaly, sometimes purpuric and rarely exfoliative. ZYLOPRIM should be withdrawn immediately should such reactions occur. After recovery from mild reactions, ZYLOPRIM may, if desired, be reintroduced at a small dose (eg. 50 mg/day) and gradually increased. If the rash recurs, ZYLOPRIM should be permanently withdrawn as more severe hypersensitivity reactions may occur.

Generalised hypersensitivity

Skin reactions associated with exfoliation, fever, lymphadenopathy, arthralgia and/or eosinophilia resembling Stevens-Johnson and/or Lyell's disease (toxic epidermal necrolysis) occur rarely. Drug rash with eosinophilia and systemic symptoms (DRESS) (drug-induced hypersensitivity syndrome

(DIHS)) also occurs rarely. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, interstitial nephritis and, very rarely, epilepsy. If such reactions do occur, it may be at any time during treatment. ZYLOPRIM should be withdrawn **immediately** and **permanently**.

Corticosteroids may be beneficial in overcoming hypersensitivity skin reactions. When generalised hypersensitivity reactions have occurred, renal and/or hepatic disorder has usually been present, particularly when the outcome has been fatal.

Very rarely acute anaphylactic shock has been reported.

Angioimmunoblastic lymphadenopathy

Angioimmunoblastic lymphadenopathy has been described rarely following biopsy of a generalised lymphadenopathy. It appears to be reversible on withdrawal of ZYLOPRIM.

Hepatic Function

Rare reports of hepatic dysfunction ranging from asymptomatic rises in liver function tests to hepatitis (including hepatic necrosis and granulomatous hepatitis) have been reported without overt evidence of more generalised hypersensitivity. Granulomatous hepatitis appears to be reversible on withdrawal of ZYLOPRIM.

Gastrointestinal

In early clinical studies, nausea and vomiting were reported. Further reports suggest that this reaction is not a significant problem and can be avoided by taking ZYLOPRIM after meals. Recurrent haematemesis has been reported as an extremely rare event as has steatorrhoea.

Haematological

Bone marrow depression has been reported in patients receiving additional medications during allopurinol therapy. However rarely has a patient receiving allopurinol alone, acquired one or more of their cell lines to be affected by bone marrow depression. There have been occasional reports of transient reduction in the numbers of circulating formed elements of the blood, usually in association with renal and/or hepatic disorder. Adverse effects such as leukocytosis, leukopenia, eosinophilia, thrombocytopenia, and granulocytopenia, have occurred very rarely. The clinical significance has yet to be demonstrated.

Other

The following complaints have been reported occasionally: fever, general malaise, asthenia, headache, vertigo, ataxia, somnolence, coma, depression, paralysis, paraesthesia, neuropathy, visual disorder, cataract, macular changes, taste perversion, stomatitis, changed bowel habit, infertility, impotence, nocturnal emission, diabetes mellitus, hyperlipidaemia, furunculosis, alopecia, discoloured hair, angina, hypertension, bradycardia, oedema, uraemia, haematuria, angioedema and gynaecomastia.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Accidental or deliberate ingestion of up to 5 g of allopurinol or very rarely 20 g, has been reported.

Symptoms: These include nausea, vomiting, diarrhoea and dizziness.

Treatment: Recovery followed general supportive measures.

Massive absorption of ZYLOPRIM may lead to considerable inhibition of xanthine oxidase activity, which should have no untoward effects unless 6-mercaptopurine and/or azathioprine is being taken concomitantly. Adequate hydration to maintain optimum diuresis facilitates excretion of allopurinol and its metabolites. If considered necessary, haemodialysis may be used.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Allopurinol inhibits xanthine oxidase, the enzyme which catalyses the conversion of hypoxanthine to xanthine, and of xanthine to urate/uric acid.



Allopurinol decreases urate formation in two ways:

1. The inhibition of xanthine oxidase reduces the amount of hypoxanthine and xanthine converted to urate/uric acid.
2. This action makes more hypoxanthine and xanthine available for reutilisation in the purine metabolic cycle, which in turn, by a feedback mechanism, decreases overall de novo purine formation.

Since allopurinol decreases urate formation, it reduces urate/uric acid concentrations in both body fluids and urine. In contrast, the uricosuric agents which increase urate/uric acid excretion via the kidney will reduce the urate concentration in body fluids, but increase urate/uric acid concentration in urine. Reduction of the urate concentrations in body fluids by allopurinol permits mobilisation and dissolution of urate deposits anywhere in the body, the commonest sites being those in the skin, bones, joints and kidney interstitial tissue. Therapeutic effects therefore include: the resolution of skin tophi and the healing of urate sinuses; eventual reduction in the frequency of attacks of acute gouty arthritis, improvement in joint mobility; reduction of the urate load to be excreted via the kidney; prevention and treatment of acute uric acid nephropathy; and, in the long-term, reduced risk of renal impairment by urate/uric acid and prevention and dissolution of uric acid renal stones.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Allopurinol is approximately 90% absorbed from the gastrointestinal tract.

Distribution

Allopurinol is uniformly distributed in total tissue water with the exclusion of the brain, where concentrations of the drugs are approximately 50% those of other tissues. Within muscle, small amounts of allopurinol and oxypurinol crystals have been found. Allopurinol and oxypurinol are not bound to plasma proteins. Allopurinol and oxypurinol are distributed into breast milk.

Metabolism

Allopurinol is rapidly converted in the body to the pharmacologically active principal metabolite oxypurinol and other metabolites including allopurinol riboside and oxypurinol-7-riboside. Peak plasma levels generally occur at 1.5 hours and 4.5 hours for allopurinol and oxypurinol respectively. Oxypurinol is also an inhibitor of xanthine oxidase.

Excretion

The renal clearance of hypoxanthine and xanthine is at least 10 times greater than that of uric acid. The increased xanthine and hypoxanthine in the urine have not been accompanied by problems of nephrolithiasis.

Approximately 20% of the ingested allopurinol is excreted in the faeces. Because of its rapid oxidation to oxypurinol and a renal clearance rate approximately that of glomerular filtration rate, allopurinol has a plasma half-life of about 1 to 2 hours. Little allopurinol is found in the urine 6 hours after administration. Allopurinol and oxypurinol are mainly excreted in the urine. Oxypurinol, however, has a longer plasma half-life (approximately 15.0 hours) and therefore effective xanthine oxidase inhibition is maintained over a 24 hour period with single daily doses of allopurinol. Whereas allopurinol is cleared essentially by glomerular filtration, oxypurinol is reabsorbed in the kidney tubules in a manner similar to the reabsorption of uric acid.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data is available on whether or not allopurinol has mutagenic effects within humans or animals. Cytogenetic studies show that allopurinol does not induce chromosome aberrations in human blood cells *in vitro* at concentrations up to 100 micrograms/mL and *in vivo* at doses up to 600 mg/day for mean period of 40 months.

Carcinogenicity

No data is available on whether or not allopurinol has carcinogenic effects within humans or animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each ZYLOPRIM tablet contains the excipients povidone, maize starch, lactose monohydrate, stearic acid and sodium starch glycollate (300mg strength only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

ALLOSIG 100 mg tablets are available in 200's, glass or HDPE bottle

ALLOSIG 300 mg tablets are available in 60's, PVC/Al blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

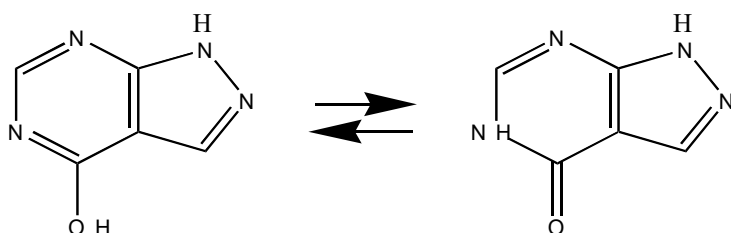
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Allopurinol has the molecular formula $C_5H_4N_4O$ with a molecular weight of 136.1. Allopurinol is a white or off-white, almost odourless powder. It is very slightly soluble in water and in alcohol, and is practically insoluble in chloroform and in ether. It dissolves in dilute solutions of alkali hydroxides.

Chemical Name: 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one.

Chemical structure



CAS number

CAS - 315-30-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Medicines Only

8 SPONSOR

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9 DATE OF FIRST APPROVAL

2 August 1991

10 DATE OF REVISION

22 May 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI reformatted to the new TGA form for providing product information format