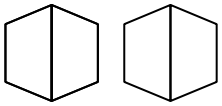
Leaflet

BIOCOXIB 90 MG and 120 MG Film Coated Tablet



COMPOSITION :

Each tablet contains : Etoricoxib 90 mg, 120 mg

PRODUCT DESCRIPTION :

BIOCOXIB 90 MG Film Coated Tablet : Asymmetric hexagonal with rounded corners, white film-coated tablets, impressed “BC” on one side and “90” on the other.

BIOCOXIB 120 MG Film Coated Tablet: Asymmetric hexagonal with rounded corners, light green film-coated tablets, impressed “BC” on one side and “120” on the other.

PHARMACOLOGY :

Pharmacodynamics

Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range. Etoricoxib produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily. It did not inhibit gastric prostaglandin synthesis and had no effect on platelet function. Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

Pharmacokinetics

Absorption

Etoricoxib is well absorbed from the gastrointestinal tract after oral doses. The absolute bioavailability is approximately 100%. Peak plasma concentrations are reached in about 1 hour in fasted adults. The pharmacokinetics of etoricoxib are linear across the clinical dose range.
Dosing with food (a high-fat meal) had no effect on the extent of absorption of etoricoxib after administration. Food delays absorption, resulting peak plasma concentrations by about 2 hours.

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 µg/ml. The volume of distribution at steady state (V_{dss}) was approximately 120 L in humans.

Metabolism

Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by CYP enzymes. CYP3A4 appears to contribute to the metabolism of etoricoxib in vivo. In vitro studies indicate that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 also can catalyse the main metabolic pathway, but their quantitative roles in vivo have not been studied.
Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Excretion

Etoricoxib is excretion mainly via the urine 70% with only 20% of a dose appearing in the feces. Less than 2% was recovered as unchanged drug.

Characteristics in patients

Elderly patients: Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young.

Gender: The pharmacokinetics of etoricoxib are similar between men and women.

Hepatic impairment: Patients with mild hepatic dysfunction (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy indivuduals given the same regimen. Patients with moderate hepatic dysfunction (Child-Pugh score 7-9) administered etoricoxib 60 mg every other day had similar mean AUC to the healthy indivuduals given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic dysfunction (Child-Pugh score ≥10).

Renal impairment: The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate to severe renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy individuals. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 ml/min).

Paediatric patients: The pharmacokinetics of etoricoxib in paediatric patients (<12 years old) have not been studied.

In adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established.

INDICATIONS :

- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis

- Treatment of acute pain including that related to primary dysmenorrhea and minor dental procedures.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see PRECAUTIONS)

DOSAGE AND ADMINISTRATION :

BIOCOXIB 90 MG and 120 MG Film Coated Tablet are administered orally. BIOCOXIB 90 MG and 120 MG Film Coated Tablet may be taken with or without food. BIOCOXIB 90 MG and 120 MG Film Coated Tablet should be administered for the shortest duration possible and the lowest effective daily dose should be used.

Osteoarthritis

The recommended dose is 30 mg or 60 mg once daily.

Rheumatoid Arthritis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Ankylosing Spondylitis

The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered.

Acute pain

In the following acute painful conditions, BIOCOXIB 90 MG and 120 MG Film Coated Tablet should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Acute Gouty Arthritis

The recommended dose is 120 mg once daily.

Primary Dysmenorrhea

The recommended dose is 120 mg once daily.

Minor Dental Procedures

The recommended dose is 90 mg once daily.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:

The dose for OA should not exceed 60 mg daily.

The dose for RA should not exceed 90 mg daily.

The dose for ankylosing spondylitis should not exceed 90 mg daily.

The dose for acute gout should not exceed 120 mg daily.

The dose for acute pain and primary dysmenorrhea should not exceed 120 mg daily.

The dose for minor dental procedures should not exceed 90 mg daily.

As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically (see PRECAUTIONS).

Elderly, Gender, Race

No dosage adjustment in BIOCOXIB 90 MG and 120 MG Film Coated Tablet is necessary for the elderly or based on gender or race.

Hepatic Insufficiency

In patients with mild hepatic insufficiency (Child-Pugh score 5-6), a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the dose should be reduced; a dose of 60 mg every other day should not be exceeded, administration of 30 mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (see PRECAUTIONS).

Renal Insufficiency

In patients with advanced renal disease (creatinine clearance <30 mL/min), treatment with BIOCOXIB 90 MG and 120 MG Film Coated Tablet is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥30 mL/min). (see PRECAUTIONS).

Biocoxib is available in only two strengths of 90 mg and 120mg. Not all approved dose regimen of Etoricoxib will be delivered; other approved dosage forms and strengths of Etoricoxib should be used in such cases.

CONTRAINDICATIONS :

BIOCOXIB 90 MG and 120 MG Film Coated Tablet contraindicated in :

- Patients with known hypersensitivity to any component of this product
- Patients with active peptic ulceration or active gastro-intestinal (GI) bleeding.
- Patients who after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors, experience bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions.
- Pregnancy and lactation
- Patients with severe hepatic dysfunction (serum albumin <25 g/l or Child-Pugh score ≥10).
- Patients with estimated renal creatinine clearance <30 ml/min.
- Children and adolescents under 16 years of age.
- Patients with inflammatory bowel disease.
- Patients with congestive heart failure (NYHA II-IV).
- Patients with established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.
- Patients who have increased risk of cardiovascular disease (ischaemic heart disease and stroke).
- Patients with hypertension (high blood pressure) whose blood pressure is not under control.

WARNING AND PRECAUTIONS :

Gastrointestinal effects :
Risk of GI Ulceration, Bleeding and Perforation with NSAID:
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.
Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding. There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when etoricoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

Cardiovascular effects :
As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with etoricoxib after careful consideration.
COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued.

Renal effects :
Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of etoricoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.

Fluid retention, oedema and hypertension :
As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking etoricoxib. All Nonsteroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.
Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib and special attention should be paid to

blood pressure monitoring during treatment with etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic effects :
Any patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, etoricoxib should be discontinued.

General :
If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered. Medically appropriate supervision should be maintained when using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction.
Caution should be used when initiating treatment with etoricoxib in patients with dehydration. It is advisable to rehydrate patients prior to starting therapy with etoricoxib.

Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Etoricoxib may mask fever and other signs of inflammation.
Caution should be exercised when co-administering etoricoxib with warfarin or other oral anticoagulants.
The use of etoricoxib, as with any medicinal product known to inhibit cyclooxygenase / prostaglandin synthesis, is not recommended in women attempting to conceive.

Warning to prescriber when prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes, smoking patient and patient with peripheral arterial disease.

DRUG INTERACTIONS :

Pharmacodynamic interactions

Oral anticoagulants :
Coadministration with BIOCOXIB 90 MG and 120 MG Film Coated Tablet may increase the risk of anticoagulant-induced bleeding (eg. GI bleeding). Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with etoricoxib is initiated or the dose of etoricoxib is changed.

Diuretics, ACE inhibitors and Angiotensin II Antagonists:
NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking etoricoxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Acetylsalicylic Acid :
Etoricoxib can be used concomitantly with acetylsalicylic acid at doses used for cardiovascular prophylaxis (low-dose acetylsalicylic acid). However, concomitant administration of low-dose acetylsalicylic acid with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Concomitant administration of etoricoxib with doses of acetylsalicylic acid above those for cardiovascular prophylaxis or with other NSAIDs is not recommended.

Cyclosporin and tacrolimus :
Although this interaction has not been studied with etoricoxib, coadministration of cyclosporin or tacrolimus with any NSAID may increase the nephrotoxic effect of cyclosporin or tacrolimus. Renal function should be monitored when etoricoxib and either of these drugs is used in combination.

Pharmacokinetic interactions

Lithium :
NSAIDs decrease lithium renal excretion and therefore increase lithium plasma levels. If necessary, monitor blood lithium closely and adjust the lithium dosage while the combination is being taken and when the NSAID is withdrawn.

Methotrexate:
Concomitant administration with BIOCOXIB 90 MG and 120 MG Film Coated Tablet may increase risk of methotrexate toxicity (eg. stomatitis, bone marrow suppression, nephrotoxicity). Adequate monitoring for methotrexate-related toxicity is recommended when etoricoxib and methotrexate are administered concomitantly.

Oral contraceptives:
Concurrent use of ethinyl estradiol (EE)/norethindrone and etoricoxib may result in increased ethinyl estradiol exposure. Use caution with the concomitant use of etoricoxib with oral contraceptives containing ethinyl estradiol as etoricoxib may increase ethinyl estradiol plasma concentrations. Consider the increased risk for adverse effects (eg, venous thromboembolic events) with higher ethinyl estradiol exposure in at-risk patients when selecting an oral contraceptive to be used concurrently with etoricoxib.

Hormone Replacement Therapy (HRT) :
Concurrent use of conjugated estrogens and etoricoxib may result in increased conjugated estrogen exposure. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with etoricoxib because the increase in estrogen exposure might increase the risk of adverse events associated with HRT.

Prednisone/prednisolone:
Concurrent use of corticosteroids and NSAIDs may result in increased risk of gastrointestinal ulcer or bleeding. If coadministration is necessary, monitor for signs of bleeding.

Digoxin:
Concurrent use of digoxin and NSAIDs may result in increased serum concentration of digoxin; prolonged half-life of digoxin. Patients at high risk of digoxin toxicity should be monitored for this when etoricoxib and digoxin are administered concomitantly.

Effect of etoricoxib on drugs metabolised by sulfotransferases :
Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1, and has been shown to increase the serum concentrations of ethinyl estradiol. While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g., oral salbutamol and minoxidil).

Effect of etoricoxib on drugs metabolised by CYP isoenzymes :
Etoricoxib is metabolized primarily by the cytochrome P450 (CYP) 3A4 isoenzyme. However, it appears to have limited inhibitory effects on CYP3A4.

Effects of other drugs on the pharmacokinetics of etoricoxib :
The main pathway of etoricoxib metabolism is dependent on CYP enzymes, extensively via CYP3A4 (in vitro data suggest that CYP2D6, CYP2C9, CYP1A2 and CYP2C19 may also play a role in metabolism).

Voriconazole and Miconazole :
Co-administration of either oral voriconazole or topical miconazole oral gel, strong CYP3A4 inhibitors, with etoricoxib caused a slight increase in exposure to etoricoxib, but is not considered to be clinically meaningful based on published data.

Rifampicin:
Concurrent administration of etoricoxib and rifampin may cause reduced etoricoxib blood concentrations. This interaction may result in recurrence of symptoms when etoricoxib is co-administered with rifampicin. While this information may require etoricoxib dose increases beyond current recommendations for each indication, and therefore is not recommended.

Antacids and Ketoconazole :
Antacids and ketoconazole (a potent inhibitor of CYP3A4) did not have clinically important effects on the pharmacokinetics of BIOCOXIB.

PREGNANCY AND LACTATION :

Pregnancy
No clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

Breastfeeding
It is unknown whether etoricoxib is excreted into human breast milk. However, etoricoxib is excreted into the milk of lactating rats. Women who use etoricoxib must not breast feed.

Fertility
The use of etoricoxib, as with any drug substance known to inhibit COX-2, is not recommended in women attempting to conceive.

ADVERSE EFFECTS:

System Organ Class	Adverse Reactions	Frequency Category
Infections and infestations	alveolar osteitis	Common
	gastroenteritis, upper respiratory infection, urinary tract infection	Uncommon
Blood and lymphatic system disorders	anaemia (primarily associated with gastrointestinal bleeding), leukopenia, thrombocytopenia	Uncommon
Immune system disorders	hypersensitivity	Uncommon
	angioedema/anaphylactic /anaphylactoid reactions including shock	Rare
Metabolism and nutrition disorders	oedema/fluid retention	Common
	appetite increase or decrease, weight gain	Uncommon
Psychiatric disorders	anxiety, depression, mental acuity decreased, hallucinations	Uncommon
	confusion, restlessness	Rare
Nervous system disorders	dizziness, headache	Common
	dysgeusia, insomnia, paresthaesia/hypaesthesia, somnolence	Uncommon
Eye disorders	blurred vision, conjunctivitis	Uncommon
Ear and labyrinth disorders	tinnitus, vertigo	Uncommon
Cardiac disorders	palpitations, arrhythmia	Common
	atrial fibrillation, tachycardia, congestive heart failure, non-specific ECG changes, angina pectoris, myocardial infarction	Uncommon
Vascular disorders	hypertension	Common
	flushing, cerebrovascular accident, transient ischaemic attack, hypertensive crisis, vasculitis	Uncommon
Respiratory, thoracic and mediastinal disorders	bronchospasm	Common
	cough, dyspnoea, epistaxis	Uncommon
Gastrointestinal disorders	abdominal pain	Very common
	Constipation, flatulence, gastritis, heartburn/acid reflux, diarrhea, dyspepsia/epigastric discomfort, nausea, vomiting, oesophagitis, oral ulcer	Common
	abdominal distention, bowel movement pattern change, dry mouth, gastroduodenal ulcer, peptic ulcers including	Uncommon

	gastrointestinal perforation and bleeding, irritable bowel syndrome, pancreatitis	
Hepatobiliary disorders	ALT increased, AST increased	Common
	hepatitis	Rare
	hepatic failure, jaundice	Rare
Skin and subcutaneous tissue disorders	ecchymosis	Common
	facial oedema, pruritus, rash, erythema, urticaria	Uncommon
	Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption	Rare
Musculoskeletal and connective tissue disorders	muscular cramp/spasm, musculoskeletal pain/stiffness	Uncommon
Renal and urinary disorders	proteinuria, serum creatinine increased, renal failure/renal insufficiency	Uncommon
General disorders and administration site conditions	asthenia/fatigue, flu-like disease	Common
	chest pain	Uncommon
Investigations	blood urea nitrogen increased, creatine phosphokinase increased, hyperkalaemia, uric acid increased	Uncommon
	blood sodium decreased	Rare

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome.

OVERDOSE AND TREATMENT :

Administration of single doses of etoricoxib up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, cardiorenal events).

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the GI tract, employ clinical monitoring, and institute supportive therapy, if required.

Etoricoxib is not dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

STORAGE CONDITION

Do not store above 30^{o}C

PACK SIZE

BIOCOXIB 90 MG Film Coated Tablet : Alu-Alu blister as packed of 5x5’s and 3x10’s

BIOCOXIB 120 MG Film Coated Tablet : Alu-Alu blister as packed of 3x10’s

Manufactured by
BIOLAB CO., LTD.
625 Soi 7A Bangpoo Industrial Estate,
Sukhumvit Road, Moo 4, Prakasa,
Muang, SAMUTPRAKARN, 10280
THAILAND

Product Registration Holder
Medispec (M) Sdn Bhd
No55&57, Lorong Sempadan 2,
Ayer Itam, 11400, Penang.

Date of revision
July 2021