New Zealand Data Sheet

1 REUTENOX

REUTENOX 20 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Reutenox tablet contains 20 mg of tenoxicam.

Excipient(s) with known effect: lactose

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Reutenox tablets are yellow, biconvex, oval, film coated tablets, scored on both sides.

The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reutenox is indicated for the symptomatic treatment of the following painful inflammatory and degenerative disorders of the musculoskeletal system:

- rheumatoid arthritis
- osteoarthritis
- arthrosis
- ankylosing spondylitis
- extra-articular disorders, e.g. tendinitis, bursitis, periarthritis of shoulders (shoulder-hand syndrome) or hips, strains and sprains
- post-operative pain
- acute gout
- primary dysmenorrhea.

4.2 Dose and method of administration

Dose

Adults

Undesirable effects may be minimised using the lowest effective dose for the shortest possible duration necessary to control symptoms.

For all indications except primary dysmenorrhoea, post-operative pain and acute gout, a daily dosage of 20 mg should be given at the same time of day.

The recommended dose for primary dysmenorrhoea is 20 to 40 mg once daily.

For postoperative pain the recommended dose is 40 mg once daily up to five days.

For acute attacks of gout the recommended dose is 40 mg once daily for two days followed by 20 mg once daily for a further five days.

In treatment of chronic disorders the therapeutic effect of tenoxicam is evident early in treatment and there is a progressive increase in response over time. In chronic disorders, daily doses higher than 20 mg are not recommended since this would increase the frequency and intensity of unwanted reactions without significantly increasing efficacy.

For patients needing long-term treatment a reduction to a daily oral dose of 10 mg may be tried for maintenance.

Special populations

Renal impairment
In principle, the above dosage recommendations also apply to patients suffering from kidney or liver disease. Dosage should be minimised in patients with renal impairment.

Elderly
The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Paediatric
No dosage recommendations have been established for children and adolescents due to insufficient data.

Method of administration

The tablets should be taken with a glass of water. It is preferable to take this medicine during or immediately after a meal.

4.3 Contraindications

Reutenox is contraindicated in patients with:

- known hypersensitivity to tenoxicam, or to any of the excipients listed in Section 6.1 or to other non-steroidal anti-inflammatory drugs (NSAIDs)
- asthma, or in whom salicylates or other NSAIDs induce symptoms of asthma, rhinitis or urticaria
- active or a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- haemorrhagic diathesis, as with other NSAIDs
- severe heart, hepatic or renal failure, as with other NSAIDs.

Reutenox is also contraindicated in the third trimester of pregnancy (see Section 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Reutenox is relatively contraindicated in patients with liver dysfunction.

The use of tenoxicam with concomitant NSAIDs, including cyclo-oxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2 Dosage and method of administration).

Cardiovascular and/or cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of selective cyclo-oxygenase-2 inhibitors (COX-2 inhibitors) and some NSAIDs (particularly at high doses and long-term treatment) may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with tenoxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose

should be used for the shortest possible duration (see Section 4.2 Dosage and method of administration).

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response.

Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention or heart failure.

There is no consistent evidence to suggest that concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Gastrointestinal bleeding, ulceration and perforation
GI bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs, including tenoxicam therapy. These effects can occur at any time during treatment, with or without warning symptoms, or a previous history of serious GI events. Studies have not identified any subset of patients not at risk of developing peptic ulcer and bleeding.

Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 - 6 months and in about 2 - 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism.

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal. Debilitated patients do not seem to tolerate ulceration or bleeding as well as others. Most of the fatal gastrointestinal events associated with NSAIDs occurred in the elderly and/or debilitated patients.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see Section 4.3 Contraindications) and in the elderly.

Patients with risk factors should commence treatment on the lowest dose possible. Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant low dose aspirin or other medicines likely to increase gastrointestinal toxicity (see Section 4.5 Interactions with other medicines and other forms of interaction).

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis; Crohn's disease) as their condition may be exacerbated. Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. If peptic ulceration or gastrointestinal bleeding occurs, Reutenox should be withdrawn immediately. Physicians should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants (e.g. warfarin), selective serotonin-reuptake inhibitors or anti-platelet agents (e.g. aspirin). The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events (see Section 4.5 Interactions with other medicines and other forms of interaction).

Skin reactions
Life-threatening cutaneous reactions such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning, have been reported with tenoxicam. These serious adverse effects are idiosyncratic and are independent of dose or duration of use.

Patients should be advised of the signs and symptoms of serious skin reactions and monitored closely for skin reactions. The highest risk of occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters of mucosal lesions) are present, Reutenox should be discontinued. The best results for managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspected medicine. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of tenoxicam, tenoxicam must not be restarted in this patient at any time.

Haematological effects
Tenoxicam inhibits platelet aggregation and may affect haemostasis. Reutenox has no significant influence on blood coagulation factors, coagulation time, prothrombin time or activated thromboplastin time.

Patients having coagulation disorders or receiving therapy that interferes with haemostasis should, however, be carefully observed when Reutenox is administered.

Ocular effects
Adverse eye findings have been reported with NSAIDs including tenoxicam. Thus ophthalmic evaluation is recommended for patients who develop visual disturbances.

Antipyretic effects
As known for other anti-inflammatory medicines, Reutenox may mask the usual signs of infection.

Galactose intolerance
As Reutenox contains lactose, patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Renal impairment
NSAIDs inhibit renal prostaglandin synthesis and consequently may have an undesirable effect on renal haemodynamics and on salt and water balance. It is necessary to adequately monitor the patient with a special emphasis on cardiac and renal function (BUN, creatinine, development of oedema, weight gain, etc.) when giving tenoxicam to patients with conditions that could increase their risk of developing renal failure, such as pre-existing renal disease, impaired renal function in diabetics, hepatic cirrhosis, congestive heart failure, volume depletion or concomitant treatment with potentially nephrotoxic medicines, diuretics and corticosteroids. This group of patients is at special risk in peri- and post-operative phases of major surgery due to the possibility of serious blood loss. They therefore require close monitoring in the post-operative and recovery periods.

Because of the high plasma protein binding of tenoxicam, caution is required when plasma albumin levels are markedly reduced.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

Acetylsalicylate and salicylates
Salicylates increase the clearance and volume of distribution of NSAIDs including tenoxicam by displacing them from protein binding sites and therefore decrease the mean minimum steady-state plasma concentrations of tenoxicam. Concurrent treatment with salicylate or other NSAIDs is not recommended because of increased risk of undesirable reactions.

Anti-platelet agents and selective serotonin reuptake inhibitors
There is an increased risk of gastrointestinal bleeding when anti-platelet agents and selective serotonin-reuptake inhibitors (SSRIs) are combined with NSAIDs (see Section 4.4 Special warnings and precautions for use).

Methotrexate
The co-administration of some NSAIDs and methotrexate has been associated with reduced renal tubular secretion of methotrexate, higher plasma concentrations of methotrexate, and severe methotrexate toxicity. Therefore, caution should be exercised when Reutenox is administered concurrently with methotrexate.

Lithium
As tenoxicam may decrease the renal clearance of lithium, their concomitant administration may lead to increased plasma levels and toxicity of lithium. The plasma levels of lithium should be closely monitored.

Diuretics and antihypertensives
As with NSAIDs in general, Reutenox should not be administered concurrently with potassium sparing diuretics. There is a known interaction between these two classes of compounds, which may cause hyperkalaemia and renal failure.

No clinically significant interaction between tenoxicam and furosemide was noted, but tenoxicam attenuates the blood pressure lowering effect of hydrochlorothiazide. As known from other NSAIDs, Reutenox might attenuate the antihypertensive effects of alpha-adrenergic blockers, beta-adrenergic blockers and ACE-inhibitors.

There was no clinically relevant interaction when tenoxicam was administered together with atenolol. During clinical trials no interaction was reported for patients treated concomitantly with digitalis products. Thus concurrent dosing of tenoxicam and digoxin appears to be without major risk.

Antacids and H_2-receptor antagonists
No clinically relevant interaction has been found with concomitantly administered antacids and cimetidine at the recommended dosages.

Probenecid
Co-administration of probenecid and tenoxicam treatment may increase plasma concentration of tenoxicam. The clinical significance of this observation has not been established.

Anticoagulants
No clinically relevant interaction has been found with concomitantly administered warfarin and phenprocoumon, and low molecular weight heparin at the recommended dosages. Nevertheless, as for other NSAIDs, careful monitoring is recommended when patients concomitantly receive anticoagulants.

Oral antidiabetics
The clinical effect of the oral antidiabetic medicines glibornuride, glibenclamide and tolbutamide was likewise not modified by tenoxicam. Nevertheless, as for other NSAIDs, careful monitoring is recommended when patients concomitantly receive oral antidiabetic medicines.

Cholestyramine
Cholestyramine may increase the clearance and reduce the half-life of tenoxicam.

Dextromethorphan
The concomitant administration of tenoxicam and dextromethorphan may increase the analgesic effect compared to monotherapy.

Ciclosporin
Increased risk of nephrotoxicity.

Pharmacodynamic interactions

Alcohol
There is no significant pharmacodynamic interaction between Reutenox and alcohol.

Food
The extent of absorption of tenoxicam is not influenced by food, but the rate of absorption (C_{max}) may be slower than in the fasting state.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, Reutenox should not be given unless clearly necessary. If Reutenox is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

and the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Reutenox is contraindicated during the third trimester of pregnancy.

Breastfeeding

Based on findings from single dose administration, a very small amount (mean value less than 0.3% of the dose) of tenoxicam passes into breast milk (see Section 5.2 Pharmacokinetic properties).

There is no evidence of adverse reactions in breast-fed infants of mothers taking Reutenox. Nevertheless, infants should be weaned or the medicine discontinued.

4.7 Effects on ability to drive and use machines

Patients experiencing adverse events that might affect driving or using machines, such as vertigo, dizziness or visual disturbances should refrain from driving a car or using machines.

4.8 Undesirable effects

Based on clinical trials including large numbers of patients, tenoxicam proved to be well tolerated in the recommended dose. Usually the undesirable effects reported were mild and transient. In a small proportion of patients the interruption of treatment due to undesirable effects was necessary.

The most commonly observed adverse events in association with NSAIDs are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see Section 4.4 Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see Section 4.4 Special warnings and precautions for use) have been reported following NSAIDs administration. Less frequently, gastritis has been observed.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

Common: > 1%
Uncommon: > 0.1% and < 1%
Rare: > 0.01% and < 0.1%
Very rare: < 0.01%
Not known: frequency cannot be estimated from available data

System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Very rare <1/10,000**	**Not known**
Blood and lymphatic system disorders				Anaemia, agranulocytosis, leucopoenia, thrombocytopenia
Cardiac disorders		Palpitations		Cardiac failure
Ear and labyrinth disorders		Vertigo		
Eye disorders				Visual disturbances (such as visual impairment and vision blurred)
Gastrointestinal disorders	Gastric, epigastric and abdominal pain, dyspepsia, nausea	Gastrointestinal haemorrhage (including haematemesis and melena),	Pancreatitis	Gastrointestinal perforation, exacerbation of colitis, Crohn's disease (see Section

		gastrointestinal ulcers, constipation, diarrhoea, vomiting, mouth ulceration, gastritis, dry mouth		4.4 Special warnings and precautions for use) and flatulence
General disorders and administration site conditions		Fatigue, oedema		
Hepatobiliary disorders		Increased hepatic enzymes		Hepatitis
Immune system disorders				Hypersensitivity reactions (such as dyspnoea, asthma, anaphylactic reactions, angioedema)
Metabolism and nutrition disorders		Decreased appetite		
Nervous system disorders	Dizziness, headache			Paraesthesia, somnolence
Psychiatric disorders		Sleep disorder		Confusional state, hallucinations
Renal and urinary disorders		Increased blood urea or creatinine		
Reproductive system and breast disorders				Isolated cases of female infertility have been reported with agents known to inhibit cyclo-oxygenase/prostaglandin synthesis including tenoxicam
Skin and subcutaneous tissue disorders		Pruritis, erythema, exanthema, rash, urticaria	Stevens-Johnson Syndrome, toxic epidermal necrolysis	Photosensitivity reaction
Vascular disorders				Hypertension, vasculitis

Clinical trial and epidemiological data suggest that use of selective cyclo-oxygenase-2 (COX-2) inhibitors and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Although tenoxicam has not shown to increase thrombotic events such as myocardial infarction, there are insufficient data to exclude such a risk with tenoxicam.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms
In general, patients with a NSAID overdosage are asymptomatic. NSAID overdosage causes only minor CNS or gastrointestinal disturbances.

There have been isolated reports of more serious toxicity after ingestion of substantial quantities; they include seizures, coma, renal failure and cardiorespiratory arrest may occur. Hepatic dysfunction, hypothrombobinemia and metabolic acidosis are also reported.

Treatment
In case of overdosage appropriate supportive treatment is indicated and discontinuation of the medicine, antacids and proton-pump inhibitors may be indicated. There are no specific antidotes. Dialysis does not significantly clear NSAIDs from the blood stream.

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

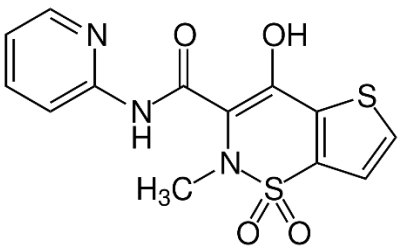
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids, Oxicams
ATC code: M01AC02

Chemistry

Chemical structure:



Mechanism of action

The active ingredient of Reutenox, tenoxicam, is a NSAID with anti-inflammatory, analgesic, antipyretic properties and it also inhibits platelet aggregation. Tenoxicam inhibits prostaglandin biosynthesis by inhibition of cyclo-oxygenase 1 (COX-1) and 2 (COX-2), both *in vitro* (sheep seminal vesicles) and *in vivo* (protection of arachidonic acid-induced toxicity in mice).

In vitro investigation on cyclo-oxygenase isoenzymes prepared from human COS-7 cells have shown that tenoxicam inhibits COX-1 and COX-2 isoenzymes approximately to the same extent i.e. COX-2/COX-1 ratio equals to 1.34.

In vitro tests of leukocyte peroxidase suggest that tenoxicam may act as a scavenger for active oxygen at the site of inflammation.

Tenoxicam is a potent *in vitro* inhibitor of human metalloproteinases (stromelysin and collagenase) which induce cartilage breakdown.

A further possible mechanism of action is the reduction of nitrite levels indicating an alteration of NO pathways.

These pharmacological effects explain, at least in part, the therapeutic benefit of Reutenox in the treatment of painful inflammatory and degenerative disorders of the musculoskeletal system.

5.2 Pharmacokinetic properties

Absorption

Oral absorption of tenoxicam is rapid and complete (absolute bioavailability 100%), whereas absorption after rectal administration is approximately 80%. Peak plasma concentrations following an oral or rectal administration are reached within two hours in fasting subjects. When taken with a meal, tenoxicam is absorbed to the same extent but the time to reach peak concentration is delayed.

With the recommended dosage regimen of 20 mg once daily, steady-state conditions are reached within ten to fifteen days without unexpected accumulation. The average concentration at steady state is 11 mg/L when tenoxicam is given at oral doses of 20 mg once daily and this does not change even on treatment for up to four years.

As predicted from single dose kinetic, plasma concentrations at steady state are 6-fold higher than those reached after a single dose.

Distribution

During the first two hours following intravenous administration of tenoxicam, plasma levels of the medicine decline rapidly.

After this short period, no difference in plasma concentrations between intravenous and oral dosing are seen. The mean volume of distribution at steady state is 10 to 12 L.

In the blood over 99% of the medicine is bound to albumin. Tenoxicam penetrates well into the synovial fluid. Peak concentrations are reached later than in plasma.

Based on findings from single dose administration a very small amount (mean value less than 0.3% of the dose) of tenoxicam passes into breast milk (see Section 4.6 Fertility, pregnancy and lactation).

Biotransformation

Tenoxicam is excreted after virtually complete biotransformation to pharmacologically inactive metabolites.

Elimination

Up to two thirds of an oral dose is excreted in the urine (mainly as the inactive 5'-hydroxytenoxicam) and the rest via the bile (a significant portion in the form of glucuronidated compounds). Less than 1% of the administered dose is recovered in the urine in form of the parent compound. The mean elimination half-life of tenoxicam is 72 hours (range 59 to 74 hours). The total plasma clearance is 2 mL/min.

Linearity

The pharmacokinetics of tenoxicam are linear in the investigated dose range of 10 to 100 mg.

Pharmacokinetics in special populations

Studies in the elderly, and in patients with renal insufficiency or liver cirrhosis suggest that no dose adjustment is necessary to achieve plasma concentrations similar to those seen in healthy subjects.

Patients with rheumatic diseases and the elderly show the same kinetics profile as healthy volunteers.

Because of the high plasma protein binding of tenoxicam, caution is required when plasma albumin levels are markedly reduced (see Section 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

Tenoxicam showed no mutagenic, carcinogenic or teratogenic effects in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Purified talc
Magnesium stearate
Hydroxypropyl methylcellulose
Polyethylene glycol 6000
Titanium dioxide
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Blister packs of 20 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 01 May 2014

10 DATE OF REVISION OF TEXT

04 March 2019

Summary table of changes

Section changed	Summary of new information
All	Datasheet re-formatted in line with SPC-style template
4.2	Minor editorial changes and re-arrangement of text
4.3	Hepatic and renal failure has been added as a contraindication
4.4	Updated to section headings
4.5	Addition of medicine interaction with ciclosporin and beta-adrenergic blockers and deletion of 'no interaction' statement between Reutenox and centrally acting alpha agonists or calcium channel blockers
4.8	Update to the frequency definitions and frequencies of undesirable effects
4.9	Update to symptoms and treatment in case of overdose
8	Change in sponsor from ABM Pharma Ltd to BNM Group