

New Zealand Data Sheet

1. Pexsig (100 mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Perhexiline maleate 100mg tablets.

Perhexiline maleate is 2-(2,2-Dicyclohexylethyl)piperidine maleate. Molecular formula is $C_{19}H_{35}N, C_4H_4O_4$ and molecular weight of 393.6.

Perhexiline maleate is a fine white crystalline powder. It is slightly soluble in water (0.1% to 1.0% w/w or 1-10mg/g). Soluble in chloroform and methanol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pexsig is a white to off-white, flat bevelled tablet, plain on one side and scored with a break line on reverse.

Diameter 8.5 mm. Each tablet contains 100 mg perhexiline maleate.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

To reduce the frequency of moderate to severe attacks of angina pectoris due to coronary artery disease in patients who have not responded to other conventional therapy or in whom such therapy may be contraindicated.

Note: Because of the serious nature of potential side effects, perhexiline maleate should be reserved for use in patients with intractable angina who are refractory or intolerant to other agents and are not suitable candidates for coronary bypass surgery.

4.2 Dose and method of administration

Adults

Commence therapy with 100 mg daily. Adjust progressively, up or down, at 2 to 4 weekly intervals based on the results of plasma level monitoring. It is generally advised not to administer more than 300 mg per day, in divided doses, but in certain cases it may be necessary to use 400 mg per day. The maintenance dose must be the minimum dose that is effective and well tolerated.

Geriatric

As for adults - see section 4.3 Contraindications.

Paediatric

Not recommended for use in children as safety and efficacy in this age group has not been established.

Monitoring of Plasma Levels

Plasma perhexiline concentrations should be maintained between 0.15 and 0.60 mcg/mL. Because of perhexiline's slow and variable clearance, the marked inter-subject variability in metabolism of the medicine and the potential for serious toxicity, regular monitoring of plasma levels of perhexiline is essential commencing at the end of the first week of use. Dosage should not be increased unless the plasma concentrations are sub-therapeutic and at least two to four weeks have elapsed since commencement, or last increase in dose, of perhexiline. If facilities for determining plasma levels are not available, Pexsig should not be prescribed.

4.3 Contraindications

Pexsig is not recommended in the presence of the following conditions:

- A history of porphyria;
- Impaired hepatic or renal function;
- Known hypersensitivity to perhexiline maleate or any of the ingredients.

If facilities for determining plasma levels are not available, Pexsig should not be prescribed.

See Monitoring of Plasma Levels under section 4.2, Dose and method of administration.

4.4 Special warnings and precautions for use**Cardiovascular effects**

The safety and efficacy of perhexiline following myocardial infarction (when clinical and laboratory findings are not stable) have not been established.

Pexsig has an effect on the ventricular conduction systems that may also have the potential of producing or aggravating ventricular conduction disturbances.

Diabetes mellitus

Pexsig should be administered with caution to patients with diabetes mellitus. Hypoglycaemia is most likely to occur in diabetic patients receiving insulin or sulphonylureas; in the majority of such patients, fasting blood sugar levels fall by approximately 30% over the first three days of therapy.

Neurological effects

In several patients on long term therapy with perhexiline, sensory, motor and autonomic neuropathy has been reported. In some cases of motor nerve dysfunction, biopsies showed denervation atrophy and demyelination. In other cases, reduced motor nerve conduction velocity, without clinical signs of peripheral neuropathy, has been reported; this change in motor nerve function was not related to the dose of perhexiline

or the duration of therapy. Other patients, in addition, had evidence of autonomic neuropathy (i.e. postural hypotension, abnormal autonomic function tests). Protein concentration in the CSF has sometimes been significantly elevated (see also section 4.8, Undesirable effects). Bilateral papilloedema, with fundal haemorrhages and both reversible and permanent impairment of visual acuity, has been reported sometimes. During the administration of Pexsig, patients must be regularly examined (at least every month) especially for the appearance of the signs or symptoms described below.

Investigation

Hepatotoxicity as manifested by an elevation in serum liver enzymes is a common adverse effect occurring during perhexiline therapy. Serum enzymes (SGPT, SGOT, ALP, LDH) should therefore be assessed prior to the commencement of treatment and at least every month thereafter.

The following clinical and laboratory observations are particularly recommended before and/or during treatment:

1. Tests for signs and symptoms of peripheral neuropathy, such as paraesthesias and muscle weakness.
2. Observation for clinical signs of hepatic involvement (weakness, loss of appetite, loss of weight).
3. Determination of serum enzymes (ALT/SGT, AST/SGOT, ALP, LDH), and bilirubin.
4. Determination of blood glucose.
5. Determination of weight.
6. Determination of plasma levels of perhexiline (see section 4.2, Dose and method of administration).

If such medical monitoring proves impractical, Pexsig should not be prescribed.

Treatment with Pexsig should be discontinued in the following instances:

1. appearance of peripheral neuropathy;
2. appearance of clinical signs of hepatic disease;
3. persistent elevations in serum enzymes or abnormalities of specific liver function tests;
4. persistent or marked hypoglycaemia;
5. excessive weight loss (see section 4.8, Undesirable effects).

Use in Renal Impairment

The use of Pexsig in patients with renal impairment is not recommended (see section 4.3, Contraindications).

Use in Hepatic Impairment

The use of Pexsig in patients with hepatic impairment is not recommended (see section 4.3, Contraindications).

Use in Children

Not recommended for use in children.

Carcinogenicity

No long-term studies in animals to evaluate the carcinogenic potential of perhexiline maleate have been conducted. Perhexiline maleate is a pyridine, and data from experimental studies indicate that pyridines represent a potential cause of cancer in man. Pyridine has been implicated in the formation of liver cancers.

Genotoxicity

Perhexiline maleate has been tested for genotoxicity in bacterial and mammalian mutation assays. Perhexiline maleate was not mutagenic in experiments with bacteria (six salmonella typhimurium strains capable of detecting G-C modifications). Weak mutagenic activity was evident in Chinese hamster V79 cells in the presence of metabolic activation. The clastogenic potential of perhexiline maleate has not been investigated.

4.5 Interaction with other medicines and other forms of interaction

Alcohol: No information available.

Food: No information available.

Other Medicines

Insulin and Antidiabetic agents: e.g. sulfonylurea:

Because hypoglycaemia has been reported in association with the administration of Pexsig, special attention must be paid with concomitant administration of products that would provoke hypoglycaemia, such as anti-diabetics and beta-blockers.

Adriamycin: Perhexiline when administered concomitantly with adriamycin when used in oncology chemotherapy may cause an increase in cell concentration leading to adriamycin toxicity.

Anticoagulants:

In an uncontrolled trial with perhexiline in 46 patients with angina pectoris, (27 receiving perhexiline combined with anticoagulants), 9 developed elevated serum transaminase levels; and 8 of these patients were taking oral anticoagulant drugs, warfarin and phenindione.

Cytochrome P450 2D6 (CY P450 2D6, CYP2D6) inhibitors or substrates:

Interaction with drugs that are either substrates or inhibitors of cytochrome CYP2D6 is possible. Caution should therefore be exercised in patients treated with perhexiline where such drugs are to be introduced, as a significant change in perhexiline blood concentration may occur.

Perhexiline blood levels should be carefully monitored to ensure blood levels remain below 0.60 µg/mL (0.6 mg/L) with dosage adjustments as required. Examples of CYP2D6 inhibitors and substrates are given below, however, this list is not meant to be exhaustive:

- Beta-adrenergic blocking agents eg. propranolol.

Because hypoglycaemia has been reported in association with the administration of Pexsig, special attention must be paid with concomitant administration of products that would provoke hypoglycaemia, such as beta-blockers.

- SSRIs e.g. fluoxetine, paroxetine and citalopram:
Cases of perhexiline toxicity have been reported with Selective serotonin (5HT) uptake inhibitors such as fluoxetine, paroxetine and citalopram. These drugs have been shown to compete with perhexiline for the hepatic cytochrome P450 2D6 (CYP 450 2D6) enzyme system.
- Tricyclic and Tetracyclic Antidepressants e.g. clomipramine hydrochloride, mirtazapine.
- Antiviral Agents: e.g. ritonavir and delavirdine.
- Antimalarials: e.g. chloroquine, proguanil and lumefantrine.
- Antinauseants, Antiemetics: e.g. ondanestron, dolasetron and metoclopramide.
- Antiarrhythmics: e.g. amiodarone and quinidine.
- Narcotic analgesics: e.g. codeine, methadone, morphine, oxycodone, pethidine and tramadol.
- Neuroleptics: e.g. haloperidol, risperidone and chlorpromazine.
- Cytotoxic drugs: e.g. tamoxifen, vinblastine, vincristine, vinorelbine, gefitinib and imatinib.

In addition: The following drugs are known substrates or inhibitors of CYP2D6: chlorpheniramine, dextromethorphan, donepezil, ethosuximide, galantamine, tolterodine, celecoxib, cimetidine, terbinafine, bupropion and moclobemide (RIMA).

Note: Pexsig has been prescribed with the following medications:

Nitroglycerin, anticoagulants, digitalis, diuretics, hypolipidaemics, antihypertensives, tranquillisers and other products. The safety of concomitant administration with these products has not yet been established, with the exception of nitroglycerin used in controlled clinical experiments. In cases where Pexsig is discontinued, and other therapy substituted, account must be taken of the half-life of the compound.

Interference with clinical laboratory tests

There may be changes in the ECG, viz slight depression of the T-wave and prolongation of the Q.T. interval. A single case of torsade de pointes has been reported.

4.6 Fertility, pregnancy and lactation

Fertility

While no teratogenic effects have been established in animal studies, treatment of male and female rats causes a reduction in fertility and treatment of pregnant rabbits and rats then causes a decrease in foetal weight and an increase in the number of resorptions.

Pregnancy

There is limited experience of the medicine's use in pregnant women and the potential benefits must be weighed against possible risks.

Perhexiline has been assigned to Category B2 in the Australian Categorisation of Risk for Medicines in Pregnancy.

The definition of Category B2:

Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Lactation

It is not known whether perhexiline maleate is excreted in breast milk and its effect on the newborn infant is unknown. Therefore, it is not recommended for nursing mothers.

4.7 Effects on ability to drive and use machines

Because of the possibility of dizziness, weakness, syncope or ataxia, caution should be used when driving vehicles or operating machinery.

4.8 Undesirable effects

Short Term (occurring after as little as 24 hours of therapy): nausea, dizziness (usually transient), hypoglycaemia in diabetic patients and torsade de pointes (very rare).

Long Term (usually occurring after ≥ 3 months of continuous treatment): peripheral neuropathy, hepatitis/cirrhosis, extrapyramidal dysfunction, muscle weakness and ataxia.

Approximately 65% of patients on perhexiline suffer adverse effects and in 7 to 8% of all patients receiving perhexiline, these are sufficiently severe to warrant discontinuing therapy. Most adverse reactions usually occur in the initial weeks of treatment. They can be transient and may disappear spontaneously in two to four weeks. More often, they recede only after the dosage is reduced, but sometimes treatment must be discontinued. In general, the appearance and severity of adverse reactions seem to be dose dependent.

Reported most often are dizziness or a "drunken" sensation, gait disorders, unsteadiness, as well as nausea, vomiting, headache, anorexia and moderate weight loss (2 to 4 kg).

Frequently reported are moderate and generally transient elevations of serum enzymes (AST/SGOT, ALT/SGPT, ALP, LDH) and bilirubin. Increases in total lipids and triglycerides, moderate hypoglycaemia and alterations of the ECG (slight depression of the T-wave and prolongation of the Q.T. interval) have also been noted.

Less frequently reported are profound weakness, nervousness, lassitude, insomnia, tremors, paraesthesias, syncope, genito-urinary disorders, changes in libido, flushing or sweating, rash or urticaria.

Rarely reported are diplopia, abdominal pain, extrapyramidal syndromes and epileptiform seizures.

Occasionally, the following more severe occurrences have been reported in patients being treated with Pexsig. Sensorimotor, polyradiculoneuritis, sometimes of a demyelination nature, which can affect the four limbs and may be accompanied by papillitis and an increase in the protein (albumin) content of the cerebrospinal fluid. This polyradiculoneuritis first appears as paraesthesias of the extremities and/or weakness of the legs with difficulty in walking.

Severe hypoglycaemia. Hypertriglyceridemia

Significant weight loss (more than 10% of initial weight) which can progress to true cachexia. Polyradiculoneuritis, hypoglycaemia and weight loss usually regress with suspension of treatment with Pexsig.

Hepatopathology including some cases of subacute alcoholic type hepatitis. Some patients have been found to have cirrhosis. The state of the liver before treatment with Pexsig, the influence of concomitant therapy or aetiological factors such as alcohol and viral hepatitis, are not known. In rare cases, hepatic damage or hypoglycaemia have led to the death of the patient.

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

Reported symptoms following overdosage are nausea and vomiting. Other symptoms that have not been reported but would be anticipated are ataxia and headache. Hepatic damage and cardiac arrhythmias may possibly occur.

Treatment

Treatment should be symptomatic and supportive. Acute perhexiline overdose should result in careful monitoring of drug levels, continuous cardiac monitoring and serial blood glucose recordings in diabetic patients. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Adequate urinary output should also be maintained.

Dialysis is not indicated because of the high degree of protein and tissue binding.

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

Perhexiline maleate is an anti-anginal agent. Its mechanism of action as an anti-anginal agent has not been fully elucidated in humans; however, *in vitro* studies suggest that perhexiline causes inhibition of myocardial fatty acid catabolism (e.g. by inhibition of carnitine palmitoyltransferase-1: CPT-1) with a concomitant increase in glucose utilisation and consequent oxygen-sparing effect. This is likely to have two consequences:

- i. increased myocardial efficiency, and
- ii. decreased potential for impairment of myocardial function during ischaemia.

The inhibition of CPT-1 is likely to contribute to the anti-ischaemic effects of perhexiline. Animal studies indicate a direct action of the medicine on the myocardium dependent in part on the marked degree of tissue binding. *In vitro* studies indicate a non-specific depressant effect of perhexiline on all smooth muscle. It also inhibits the spontaneous depolarisation of Purkinje fibres in the dog myocardium and reduces sodium and potassium conductance.

Perhexiline has a cardiac membrane effect similarly to that of quinidine and procainamide. Perhexiline, whilst it does not affect resting heart rate, has been shown to reduce exercise induced tachycardia in man. Perhexiline has also been shown to have a mild diuretic effect in man and animals.

5.2 Pharmacokinetic properties

Absorption

After oral administration, perhexiline maleate is well absorbed (>80%) from the gastrointestinal tract.

Bioavailability

Complete data on rate and extent of absorption are not available.

Distribution

There is a large volume of distribution of perhexiline that is probably related to the marked tissue binding of both perhexiline and its metabolites. Adverse effects related to the central nervous system such as vestibular and cerebellar dysfunction are presumed because it crosses the blood brain barrier. It is not known whether it enters breast milk or crosses the placenta.

Protein binding

Perhexiline and its metabolites are highly protein bound (>90%). There is also some degree of binding to red blood cells.

Metabolism

The full metabolic fate of perhexiline has not been elucidated. The principal metabolites of perhexiline in man are monohydroxyperhexiline (which is excreted, in part, conjugated with glucuronic acid) and

dihydroxyperhexiline that accounts for a relatively small proportion of the total metabolites. Two unidentified metabolites have also been found in the faeces. The pharmacological activity of the metabolites is not known.

Excretion

Perhexiline and its metabolites are cleared from the body via extensive hepatic metabolism to mono- and dihydroxyperhexilines, and are excreted in the bile and urine in a ratio of 1:2.

Hydroxylation of perhexiline is controlled by cytochrome P450 2D6 (CY P450 2D6). Approximately 7% of Caucasians are poor hydroxylators, and usually clear perhexiline at approximately 10% of the rate of normal metabolisers. A few patients are ultrafast hydroxylators and require increased steady-state doses of perhexiline. Even in normal metabolisers, the clearance of perhexiline is readily saturable within the clinical dose range. This results in disproportionate changes in steady-state plasma perhexiline concentration per unit change in daily dose.

Half-life

Because of its non-linear metabolism, perhexiline cannot strictly be said to have a half-life at perhexiline concentrations normally measured in plasma. It is a relatively long acting medicine with marked variation in rate of elimination between individuals. In the majority of patients, the medicine behaves as if it has a half-life of two to six days. In a small number of individuals, this may increase to greater than thirty days.

Note

While longer term studies have not been carried out, it is possible that, with continuing treatment, the metabolism and excretion of perhexiline may be altered. Studies in man have shown that in the first 1 to 2 weeks no unchanged perhexiline is detected in the urine but after that unaltered medicine appears in the urine in all subjects.

Clinical significance of pharmacokinetics

As a result of the marked variations in clearance, three types of population have been suggested: namely, fast, intermediate and slow metabolisers.

There is a wide range of variation between individuals in the daily levels of perhexiline (0.29 to 3.8mcg/ml on a 400mg per day of perhexiline) and no studies have established the time taken to reach steady state conditions. However, it is likely that steady state blood levels will be achieved only after two to four weeks of therapy, and after longer periods in some patients. This time period should be borne in mind when dosage adjustment is being considered.

In view of the above and considering the tissue binding occurs to a marked degree with both perhexiline and its metabolites (the pharmacological activity of the latter is unknown), accumulation with increased toxicity may result and could be a contributing factor in causing neuropathy.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, sucrose and purified talc.

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months from the date of manufacture when stored below 30°C.

6.4 Special precautions for storage

Store in cool dry place below 30°C.

6.5 Nature and contents of container

Bottles (glass) containing 100 tablets.

6.6 Special precautions for disposal (and other handling)

No data available.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Limited Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland

9. DATE OF FIRST APPROVAL

12 October 2009

10. DATE OF REVISION OF THE TEXT

21 April 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
Format of Data sheet	As per new European SmPC style format
6.1	Excipient changed to lactose monohydrate.