

# NEW ZEALAND DATA SHEET

## 1 LUDIOMIL

Maprotiline hydrochloride 25 mg and 75 mg film coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets contain 25 mg or 75 mg of Maprotiline hydrochloride

## 3 PHARMACEUTICAL FORM

Ludiomil® 25 mg are round, grey-orange tablets with a white core, diameter 6.1 mm, with slightly convex faces and slightly bevelled edges. The tablets are imprinted DP and a score on one side. Each tablet contains 25 mg maprotiline hydrochloride.

Ludiomil® 75 mg are round, brown-red tablets with a white core, diameter 8.1 mm, with slightly convex faces and slightly bevelled edges. The tablets are imprinted FS with score on one side. Each tablet contains 75 mg maprotiline hydrochloride.

Do not halve the 75 mg tablets. Dose equivalence when the 75 mg tablet is divided has not been established. Tablets should be swallowed whole with sufficient liquid.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Depression
- Endogenous and late-onset (involutional) depression.
- Psychogenic, reactive, and neurotic depression, exhaustion depression.
- Somatogenic depression.
- Masked depression.
- Menopausal depression.
- **Other depressive mood disorders** characterised by anxiety, dysphoria, or irritability; apathetic states (especially in the elderly); psychosomatic and somatic symptoms with underlying depression and/or anxiety.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) are standard classifications of mental disorders used by mental health professionals and describe the above mentioned disorders as follows: Treatment of depressive episodes, recurrent depressive disorder or major depression.

### 4.2 Dose and method of administration

During treatment with Ludiomil® the patient should be kept under medical surveillance.

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The recommended dose range is between 75 and 150 mg daily. Depending on the severity of the symptoms, patient response and tolerance, the daily dose may start at 25 mg (one to three times daily) or 75 mg (once daily) then gradually titrated up to the effective dose. Daily doses above 150 mg are not recommended.

The dosage schedule should be determined individually and adapted to the patient's condition and response, e.g. by increasing the evening dose while lowering the doses given during the day or, alternatively, by administering only one daily dose. The aim is to achieve a therapeutic effect using the lowest possible doses, particularly in patients who are still growing or elderly patients with an unstable autonomic nervous system, since these patients are generally more likely to experience adverse events.

Ludiomil® tablets should be swallowed whole with sufficient liquid. Do not halve the 75 mg tablets. Dose equivalence when the 75 mg tablet is divided has not been established.

### Elderly patients (more than 60 years of age)

In general, lower dosages are recommended. Initially, 10 mg 3 times daily or 25 mg once daily. If necessary, the daily dosage should be gradually increased in small increments up to 25 mg 3 times daily or 75 mg once daily, depending on tolerance and response.

### Children and adolescents (less than 18 years of age)

The safety and efficacy of Ludiomil® in children and adolescents have not been established. Use in this age group is therefore not recommended.

### Treatment discontinuation

Abrupt withdrawal or abrupt dose reduction should be avoided because of possible adverse reactions.

### 4.3 Contraindications

- Hypersensitivity to maprotiline, any of the excipients (see section 6.1), or cross-sensitivity to tricyclic antidepressants.
- Convulsive disorder or a lowered convulsion threshold (e.g. brain damage of varying aetiology, alcoholism).
- Acute stage of myocardial infarction and cardiac conduction defects (including congenital long QT syndrome).
- Severe hepatic or renal impairment.
- Narrow-angle glaucoma or urinary retention (e.g. due to prostatic disease).
- Concomitant treatment with a MAO inhibitor (see section 4.5).
- Acute poisoning with alcohol, hypnotics, or psychotropic agents (see section 4.5).
- Ludiomil® is contraindicated for the treatment of depression in children and adolescents.
- Ludiomil® is contraindicated for the treatment of nocturnal enuresis.

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### 4.4 Special warnings and precautions for use

#### Antiarrhythmics

Antiarrhythmics that are potent inhibitors of CYP2D6, such as quinidine and propafenone, should not be used in combination with Ludiomil®. The anticholinergic effects of quinidine may cause dose-related synergism with Ludiomil® (see section 4.5).

#### Clinical Worsening and Suicide/suicidal thoughts Risk:

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases.

It has been the general clinical experience that the risk of suicide increases in the early stages of recovery. In patients with a history of suicidal events, or those at high risk of suicide prior to commencement of therapy, the risk of suicidal ideation or suicide attempts is increased. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicide compared with placebo in patients who are younger than 25 years.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. In adults and children with depressive disorders, worsening of depression and/or suicidal ideation or other psychiatric symptoms can occur regardless of whether they received treatment with antidepressants. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

In short-term studies in children and adolescents and young adults under 25 years with depressive disorders and other psychiatric disorders, antidepressants increased the risk of suicidal ideation and behaviour (suicidality).

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It is particularly important that careful monitoring be undertaken, especially in those patients who have an increased risk during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Ludiomil® should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### Mania and Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that

Ludiomil® is not approved for use in treating bipolar depression.

### Information for Patients and Families

Patients and their families should be alerted about the need to monitor for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's doctor, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicines efficacy and safety when used in the treatment regimen proposed.

### Convulsions

There have been rare reports of convulsions occurring in patients without a history of convulsions who were treated with therapeutic doses of Ludiomil®. In some cases other confounding factors were present, such as concomitant medications known to lower the convulsion threshold. The risk of convulsions may be increased when antipsychotics (e.g. phenothiazines, risperidone) are given concomitantly (see section 4.5), when concomitant administration of benzodiazepines is interrupted abruptly, or when the recommended dosage of Ludiomil® is rapidly exceeded. While a causal relationship has not been established, the risk of convulsions may be reduced by: using low starting doses; maintaining the initial dosage for 2 weeks and then raising it gradually in small increments; keeping the maintenance dose at the minimum effective level; cautious adjustment or avoidance of co-medication with medicinal products that lower the convulsion threshold (e.g. phenothiazines, risperidone), or rapid discontinuation of benzodiazepines is avoided.

Concomitant electroconvulsive therapy should be carried out only under careful supervision.

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### Cardiac and vascular disorders

Use with caution in patients with severe cardiovascular disease including heart failure, conduction disorders (e.g. AV block grades I to III) or cardiac arrhythmia. Cardiovascular and ECG monitoring should be undertaken in such patients. An ECG should be performed prior to starting treatment, at steady state, after an increase in dose or after starting any potentially interacting medicine.

Maprotiline should be used with caution in patients with risk factors for QTc prolongation/TdP including congenital long QT syndrome, age > 65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of maprotiline, and the concomitant use of other QTc prolonging medicines (see section 4.5). Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

Consideration should be given to stopping maprotiline treatment or reducing the dose if the QTc interval is > 500 ms or increased by > 60 ms.

Tricyclic and tetracyclic antidepressants have been reported to produce cardiac arrhythmias, sinus tachycardia and prolongation of conduction time. Ventricular tachycardia, ventricular fibrillation, and Torsade de Pointes have very rarely been reported in patients treated with Ludiomil® some of these cases have been fatal. Caution is indicated in elderly patients and patients with cardiovascular disease, including a history of myocardial infarction, arrhythmias and/or ischaemic heart disease. Monitoring of cardiac function, including ECG, is indicated in such patients, especially during long-term treatment. Regular measurement of blood pressure is called for in patients susceptible to orthostatic hypotension.

### Other psychiatric effects

Activation of psychosis has occasionally been observed in patients with schizophrenia receiving tricyclic antidepressants and must be considered a risk with Ludiomil® a tetracyclic antidepressant. Similarly, hypomanic or manic episodes have been reported in patients with bipolar disorders while under treatment with a tricyclic antidepressant during a depressive phase. In such cases it may be necessary to reduce the dosage of Ludiomil® or to withdraw it and administer an antipsychotic agent. Co-medication with antipsychotics (e.g. phenothiazines, risperidone) may result in increased plasma levels of maprotiline, a lowered convulsion threshold and convulsions (see section 4.5). Combination with the CYP2D6 inhibitor thioridazine may produce severe cardiac arrhythmia. Dose adjustment may therefore be necessary.

In predisposed and elderly patients, tricyclic antidepressants may provoke pharmacogenic (delirious) psychoses, especially at night; these disappear without treatment within a few days of withdrawal.

Patients taking Ludiomil® should be warned that their response to alcohol, barbiturates and other CNS depressants may be intensified (see section 4.5).

### Hypoglycaemia

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The possibility of hypoglycaemia should be considered in patients receiving Ludiomil® concomitantly with oral sulfonylureas or insulin. Diabetic patients should closely monitor their blood glucose when treatment with Ludiomil® has been initiated or discontinued (see section 4.5).

### White blood cell count

Although changes in the white blood cell count have been reported with Ludiomil® only in isolated cases, periodic blood cell counts and monitoring for symptoms such as fever and sore throat are called for, particularly during the first few months of therapy. They are also recommended during prolonged therapy.

### Anaesthesia

Before general or local anaesthesia, the anaesthetist should be informed that the patient has been receiving Ludiomil®. It is safer to continue treatment than to risk disruption due to discontinuation before surgery.

### Specific treatment populations and long-term treatment

During long-term treatment it is advisable to monitor hepatic and renal function.

Caution is recommended in patients with liver and kidney damage, as well as in patients with a history of increased intraocular pressure, pheochromocytoma, chronic severe constipation or a history of urinary retention, particularly in the presence of prostatic hypertrophy.

Cyclic antidepressants may give rise to paralytic ileus, particularly in the elderly and in hospitalised patients. Appropriate measures should therefore be taken if constipation occurs.

Caution is recommended in hyperthyroid patients and patients on thyroid-hormone preparations (possible increase in unwanted cardiac effects).

An increase in dental caries has been reported in patients receiving long-term treatment with cyclic antidepressants. Regular dental checks are therefore advisable during long-term therapy (see section 4.8).

Decreased lacrimation and relative accumulation of mucoid secretion associated with the anticholinergic properties of cyclic antidepressants may cause damage to the corneal epithelium in patients who wear contact lenses.

This medicinal product is not recommended in combination with clonidine, guanfacine, or alpha- or beta-sympathomimetics (adrenaline, noradrenaline or dopamine administered parenterally) (see section 4.5).

Ludiomil® can increase skin sensitivity to sunlight. Even brief exposure to the sun can cause skin rash, itching, redness or discoloration (see section 4.8). In the case of direct exposure to sunlight, patients should wear sunglasses and protect themselves by wearing the appropriate clothing.

It has been reported that, in terms of its association with a fatal overdose, Ludiomil® is comparable to other antidepressants

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## Treatment discontinuation

Abrupt withdrawal or abrupt dose reduction should be avoided because of possible adverse reactions. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (section 4.8 - for a description of the risks of withdrawal of Ludiomil®).

## Lactose

Ludiomil® tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicines and other forms of interaction

### CYP2D6 inhibitors

Concomitant administration of CYP2D6 inhibitors may lead to an increase in concentration of maprotiline, up to ~3.5-fold in patients with a debrisoquine extensive metaboliser phenotype, converting them to a poor-metaboliser phenotype (see section 5.2).

### Medicines that can prolong the QTc interval

The risk of QTc prolongation and/or ventricular arrhythmias, including ventricular tachycardia and (e.g. Torsades de pointes (TdP) is increased with concomitant use of other medicines which prolong the QTc interval (e.g. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval. Caution is recommended while administering drug that prolong the QT interval, especially in patients with underlying risk factors.

### MAO inhibitors

Monoamine oxidase (MAO) inhibitors that are potent CYP2D6 inhibitors in vivo, such as moclobemide, are contraindicated for co-administration with Ludiomil® (see section 4.3). Ludiomil® must not be given for at least 14 days after discontinuation of treatment with MAO inhibitors to avoid the risk of severe interactions such as hyperpyrexia, tremor, generalised clonic convulsions, delirium, and possible death. The same applies when giving an MAO inhibitor after previous treatment with Ludiomil® (see section 4.3).

### Antiarrhythmics

Antiarrhythmics that are potent inhibitors of CYP2D6, such as quinidine and propafenone, should not be used in combination with Ludiomil®. The anticholinergic effects of quinidine may cause dose-related synergism with Ludiomil®.

### Antidiabetic agents

Co-medication with oral sulfonylureas or insulin may potentiate the hypoglycaemic effect of antidiabetic agents. Diabetic patients should monitor their blood glucose when treatment with Ludiomil® has been initiated or discontinued (see section 4.4).

### Antipsychotics

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Co-medication with antipsychotics (e.g. phenothiazines, risperidone) may result in increased plasma levels of maprotiline, a lowered convulsion threshold and convulsions. Combination with the CYP2D6 inhibitor thioridazine may produce severe cardiac arrhythmia. Dose adjustment may therefore be necessary.

### Anticoagulants

Some tricyclic antidepressants may potentiate the anticoagulant effect of coumarin, possibly by inhibition of its metabolism in liver or decreased intestinal motility. There is no evidence of the ability of Ludiomil® to inhibit the metabolism of anticoagulants such as warfarin (active S-enantiomer cleared by CYP2C9), but careful monitoring of plasma prothrombin is recommended for this class of substances.

### Anticholinergic agents

Ludiomil® may potentiate the effects of anticholinergic agents (e.g. phenothiazines, antiparkinson agents, atropine, biperiden, antihistamines) on the pupils, central nervous system (CNS), bowel and bladder.

### Antihypertensive agents

Concomitant administration of beta blockers that are inhibitors of CYP2D6, such as propranolol, may cause an increase in plasma maprotiline concentrations. In such cases, monitoring of plasma levels and adjustment of the dosage is recommended.

Ludiomil® may diminish or abolish the antihypertensive effects of antiadrenergic agents such as guanethidine, bethanidine, reserpine, clonidine and alpha-methyldopa. Patients requiring comedication for hypertension should therefore be given antihypertensives of a different type (e.g. diuretics, vasodilators, or beta blockers that do not undergo pronounced biotransformation). Sudden withdrawal of Ludiomil® can also result in serious hypotension.

### Sympathomimetic agents

Ludiomil® may potentiate the cardiovascular effects of sympathomimetic agents such as adrenaline, noradrenaline, isoprenaline, ephedrine and phenylephrine, as well as of decongestants and local anaesthetics (e.g. those used in dentistry). Close supervision (blood pressure, cardiac rhythm) and careful dosage adjustment are therefore required.

### Central nervous system depressants

Patients taking Ludiomil® should be warned that their response to alcohol, barbiturates and other CNS depressants may be intensified (see section 4.4).

### Benzodiazepines

Co-medication with benzodiazepines may cause increased sedation.

### Methylphenidate

Methylphenidate may increase plasma concentrations of tricyclic antidepressants and so intensify their effects. Dose adjustment may therefore be necessary.

### SSRIs

Selective serotonin reuptake inhibitors (SSRIs) that are inhibitors of CYP2D6, such as fluoxetine, fluvoxamine (also an inhibitor of CYP3A4, CYP2C19, CYP2C9, and CYP1A2),



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paroxetine, sertraline or citalopram, may result in highly increased plasma maprotiline concentrations, with corresponding side effects. Due to the long half-life of fluoxetine and fluvoxamine, this effect may be prolonged. Dose adjustment may therefore be necessary.

### H<sub>2</sub>-receptor antagonists

Although not reported with Ludiomil<sup>®</sup>, co-administration with the histamine<sub>2</sub> (H<sub>2</sub>)- receptor antagonist cimetidine (an inhibitor of several P450 enzymes, including CYP2D6 and CYP3A4) has been shown to inhibit the metabolism of several tricyclic antidepressants, resulting in increased plasma concentrations of the latter and an increase in unwanted effects (dry mouth, disturbed vision). It may therefore be necessary to reduce the dosage of Ludiomil<sup>®</sup> when given concomitantly with cimetidine.

### Oral antifungal, terbinafine

Concomitant administration of terbinafine, an antifungal drug (a potent inhibitor of CYP2D6) may result in increased plasma levels of maprotiline. Dose adjustment of Ludiomil<sup>®</sup> may be necessary.

### Other interactions

Interactions may occur with antiretroviral drugs, antiprotozoals (e.g. quinine), dihydroergotamines, disulfiram and muscle relaxants (e.g. baclofen). Elevated exposure of maprotiline may occur when co-administered with antiretrovirals as they might inhibit CYP2D6. Similarly, quinine which inhibits CYP2D6, should not be given at the same time as maprotiline, as there is an increased risk of arrhythmias. Disulfiram might inhibit the biotransformation of maprotiline and therefore, levels of maprotiline should be monitored if patients are taking this in combination with disulfiram. Maprotiline might enhance the effects of muscle relaxants.

### Effect of cytochrome P450 inducers on maprotiline metabolism

Maprotiline is primarily metabolised by CYP2D6, and to some extent by CYP1A2. CYP2D6 has not been found to be inducible, but concomitant administration of substances known to induce CYP1A2 may increase the formation of desmethylmaprotiline and reduce the effectiveness of Ludiomil<sup>®</sup>. The overall pharmacodynamic effect is not expected to be reduced, as this metabolite is active. However, induction of enzymes yet to be identified in the deactivation of maprotiline and desmethylmaprotiline (e.g. P450s, phase II enzymes) may accelerate the clearance of the active components and decrease the efficacy of Ludiomil<sup>®</sup>. Adjustment of Ludiomil<sup>®</sup> dosage may be necessary when administered concomitantly with substances that induce hepatic cytochrome P450s, particularly those typically involved in tricyclic antidepressant metabolism, such as CYP3A4, CYP2C19, and/or CYP1A2 (e.g. rifampicin, carbamazepine, phenobarbital, and phenytoin).

## 4.6 Fertility, pregnancy and lactation

### Fertility

No special recommendations.

### Women of child-bearing potential

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No special recommendations.

### Pregnancy

Animal experiments showed no teratogenic or mutagenic effects and no evidence of impaired fertility or harm to the foetus. However, safe use during pregnancy has not been established. Isolated cases suggesting a possible association between Ludiomil® and adverse effects on the human foetus have been reported. Ludiomil® should not be administered during pregnancy unless the benefits clearly outweigh the risk to the foetus.

Ludiomil® should be given to pregnant women only if clearly needed.

Ludiomil® should be withdrawn at least 7 weeks before the expected date of delivery, provided the clinical status of the patient permits, to prevent possible symptoms such as dyspnoea, lethargy, irritability, tachycardia, hypotonia, convulsions, jitter and hypothermia in the new-born.

### Lactation

Maprotiline passes into the breast milk. After oral administration of 150 mg daily for 5 days, concentrations in the breast milk exceed blood concentrations by a factor of 1.3 to 1.5. Although reports have shown no adverse effects on the infant, mothers receiving Ludiomil® should not breast-feed.

#### 4.7 Effects on ability to drive and use machines

Patients receiving Ludiomil® should be warned that blurred vision, dizziness, somnolence and other CNS symptoms (see section 4.8) may occur, in which case they should not drive, operate machinery, or engage in other potentially dangerous activities. Patients should also be warned that consumption of alcohol or other medicinal products may potentiate these effects.

#### 4.8 Undesirable effects

Adverse effects are usually mild and transient, disappearing with continued treatment or following a reduction in the dosage. They do not always correlate with plasma drug levels or with dose. It is often difficult to distinguish certain adverse effects from symptoms of depression such as fatigue, sleep disturbances, agitation, anxiety, constipation or dry mouth.

In the event of serious adverse reactions, e.g. of a neurological or psychiatric nature, Ludiomil® should be withdrawn.

Elderly patients are particularly sensitive to anticholinergic, neurological, psychiatric or cardiovascular effects. Their ability to metabolise and eliminate substances may be reduced, leading to risk of elevated plasma concentrations at therapeutic doses (see sections 4.2 and 5.2).

The following adverse effects have been reported either with Ludiomil® or with tricyclic antidepressants.

Table 1

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Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ) uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), including isolated reports, not known (frequency cannot be estimated from the available data).

<b>Blood and lymphatic system disorders</b>	
Very rare:	Leukopenia, agranulocytosis, eosinophilia, thrombocytopenia.
<b>Endocrine disorders</b>	
Very rare:	Inappropriate antidiuretic hormone secretion (SIADH).
<b>Metabolism and nutrition disorders</b>	
Common:	Increased appetite, abnormal weight gain.
Very rare:	Hyponatraemia
<b>Psychiatric disorders</b>	
Common:	Restlessness, anxiety, agitation, mania, hypomania, libido disorder, aggression, sleep disorder, insomnia, nightmare, depression.
Rare:	Delirium, confusional state, hallucination (particularly in geriatric patients), nervousness.
Very rare:	Psychotic disorder, depersonalisation.
Not known:	Suicidal ideation and behaviour (case reports of suicidal ideation and behaviour were reported during treatment or shortly after completion of the treatment of maprotiline) (see section 4.4)
<b>Nervous system disorders</b>	
Very common:	Somnolence, dizziness, headache, mild tremor, myoclonus.
Common:	Sedation, memory impairment, disturbance in attention, paraesthesia (numbness, tingling), dysarthria.
Rare:	Convulsion, akathisia, ataxia.
Very rare:	Dyskinesia, coordination abnormal, syncope, dysgeusia, balance disorder.
<b>Eye disorders</b>	
Common:	Vision blurred, accommodation disorder
<b>Ear and labyrinth disorders</b>	
Very rare:	Tinnitus.

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<b>Cardiac disorders</b>	
Common:	Sinus tachycardia, palpitations.
Rare:	Arrhythmia.
Very rare:	Conduction disorder (e.g. widening of QRS complex, bundle branch block, PQ changes), ventricular tachycardia, ventricular fibrillation, torsade de pointes.
<b>Vascular disorders</b>	
Common:	Hot flush, flushing, orthostatic hypotension.
<b>Respiratory, thoracic and mediastinal disorders</b>	
Very rare:	Alveolitis allergic (with or without Eosinophilia, interstitial lung disease, e.g. subacute interstitial pneumonitis), bronchospasm, nasal congestion.
<b>Gastrointestinal disorders</b>	
Very common:	Dry mouth.
Common:	Nausea, vomiting, abdominal disorders, constipation.
Rare:	Diarrhoea.
Very rare:	Stomatitis, dental caries.
<b>Hepatobiliary disorders</b>	
Very rare:	Hepatitis (with or without jaundice)
<b>Skin and subcutaneous tissue disorders</b>	
Common:	Dermatitis allergic, (rash, urticaria), photosensitivity reaction, hyperhidrosis.
Very rare:	Pruritus, cutaneous vasculitis, alopecia, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, purpura.
<b>Musculoskeletal, connective tissue and bone disorders</b>	
Common:	Muscular weakness.
<b>Renal and urinary disorders</b>	
Common:	Micturition disorder.
Very rare:	Urinary retention.
<b>Reproductive system and breast disorders</b>	
Common:	Erectile dysfunction.
Very rare:	Breast enlargement, (gynaecomastia), galactorrhoea.
Not known	Sexual dysfunction
<b>General disorders and administration site conditions</b>	
Very common:	Fatigue
Common:	Pyrexia.
Very rare:	Oedema (local or generalised).

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<b>Investigations</b>	
Common:	Weight increased, electrocardiogram abnormal (e.g. ST and T wave changes), intraocular pressure increased
Rare	Blood pressure increased, liver function test abnormal (transaminases, alkaline phosphatase).
Very rare:	Electroencephalogram abnormal, electrocardiogram QT prolonged.
<b>Injury, poisoning and procedural complications</b>	
Very rare:	Fall
Not known:	Fractures Epidemiological studies, mainly conducted in patients who were aged 50 years or older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The mechanism that leads to this risk is unknown.

### Withdrawal symptoms

Although not indicative of addiction, the following symptoms occasionally occur after abrupt withdrawal or reduction of the dose: nausea, vomiting, abdominal pain, diarrhoea, insomnia, headache, nervousness, anxiety, worsening of underlying depression or recurrence of depressed mood (see section 4.4).

**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

The signs and symptoms of overdose with Ludiomil® are similar to those reported with tricyclic antidepressants. Cardiac abnormalities and neurological disturbances are the main complications. In children accidental ingestion of any amount should be regarded as serious and potentially fatal.

Symptoms generally appear within 4 hours of ingestion and reach maximum severity at 24 hours. Due to delayed absorption (anticholinergic effect), long half-life, and enterohepatic recycling, the patient may remain at risk for up to 4 to 6 days.

The following signs and symptoms occur.

Central nervous system: somnolence, stupor, coma, ataxia, restlessness, agitation, enhanced reflexes, muscular rigidity and choreo-athetotic movements, convulsions.

Cardiovascular system: hypotension, tachycardia, QTc prolongation, arrhythmias, conduction disorders, shock, heart failure; ventricular tachycardia, ventricular fibrillation, Torsade de Pointes, cardiac arrest, some of which have been fatal. In addition, respiratory depression, cyanosis, vomiting, fever, mydriasis, sweating, and oliguria or anuria may occur.

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### Treatment

There is no specific antidote and treatment is essentially symptomatic and supportive.

Patients, particularly children, who may have ingested an overdose of Ludiomil® should be hospitalised and kept under close surveillance for at least 72 hours.

The stomach should be emptied as quickly as possible by lavage, or induced emesis if the patient is alert. If the patient is not alert, the airway should be secured with a cuffed endotracheal tube before beginning lavage, and emesis should not be induced. These measures are recommended for up to 12 hours or even longer after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help to reduce drug absorption.

Symptomatic treatment is based on modern methods of intensive care with continuous monitoring of cardiac function, blood gases and electrolytes, and possible need for emergency measures, such as anticonvulsive therapy, artificial respiration, and resuscitation. Physostigmine has been reported to cause severe bradycardia, asystole and convulsions, and its use is therefore not recommended in cases of overdosage with Ludiomil®. Haemodialysis and peritoneal dialysis are ineffective because of the low plasma concentrations of maprotiline.

Alkalinisation with sodium bicarbonate or sodium lactate plasma has proved successful in the treatment of cardiac complications. A clinical-toxic test of the blood or plasma is recommended.

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

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## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC code: N06AA21

Maprotiline hydrochloride is a tetracyclic antidepressant, psychoanaleptics, non-selective mono-amine reuptake inhibitor, which shares a number of basic therapeutic properties with the tricyclic antidepressants. It displays a well-balanced spectrum of action, brightening mood and alleviating anxiety, agitation and psychomotor retardation. In masked depression, it can exert a favourable influence on somatic symptoms.

Maprotiline differs structurally and pharmacologically from the tricyclic antidepressants. It has a potent and selective inhibitory effect on noradrenaline re-uptake in the pre-synaptic neurons of cortical structures in the central nervous system but exerts hardly any inhibitory effect on serotonin re-uptake. Maprotiline shows weak to moderate affinity for central alpha1- adrenoceptors, marked inhibitory activity at histamine H1 receptors and a moderate anticholinergic effect.

Changes in functional responsiveness of the neuroendocrine system (growth hormone, melatonin, endorphinergic system) and/or neurotransmitters (noradrenaline, serotonin, GABA) during long-term treatment are also considered to be involved in the mechanism of action.

### 5.2 Pharmacokinetic properties

#### Absorption

Following single oral administration of film-coated tablets, maprotiline hydrochloride is slowly but completely absorbed. The mean absolute bioavailability is approximately 66 to 70%. Within 8 hours of a single oral dose of 50 mg, peak blood concentrations of 48 to 150 nmol/L (13 to 47 ng/mL) are attained.

After repeated oral or intravenous administration of 150 mg Ludiomil® daily, steady-state blood concentrations of 320 to 1270 nmol/L (100 to 400 ng/mL) are reached during the second week of treatment, whether the amount is given in a single dose or in three fractional doses. Steady-state levels of maprotiline are in linear proportion to the dose, although the concentrations vary greatly from one subject to another.

Peak Plasma concentration is reached after 8-24 hours.

#### Distribution

The partition coefficient of maprotiline between blood and plasma is 1.7. The mean apparent distribution volume is 23 to 27 L/kg. Maprotiline is 88 to 90% bound to plasma proteins, independent of the patient's age or disease. Concentrations in cerebrospinal fluid are 2 to 13 % of serum concentrations.

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### Biotransformation

Maprotiline is primarily eliminated through metabolism; only 2 to 4 % of the dose is excreted unchanged in the urine. The principal route of metabolism is the formation of the pharmacologically active metabolite, desmethylmaprotiline. Of minor importance are several hydroxylated and/or methoxylated metabolites, which are excreted as conjugates by the kidney. Primary elimination of maprotiline and desmethylmaprotiline is through hydroxylation and further conjugation of the metabolites and excretion in the urine. The hydroxylated metabolites, such as isomeric phenols, 2- and 3-hydroxymaprotiline and 2, 3-dihydrodiol, represent only 4 to 8% of the dose excreted in human urine. The majority of the eliminated products are glucuronide conjugates of the primary metabolites (75%). The demethylation of maprotiline appears to be catalysed primarily by CYP2D6, with some contributions by CYP1A2.

### Elimination

Maprotiline is eliminated from the blood with a mean half-life of approximately 43 to 45 hours. Mean systemic clearance ranges between 510 and 570 mL/min.

Within 21 days, about two thirds of a single dose are excreted in urine, predominantly as free and conjugated metabolites, and about one third in the faeces.

### Linearity / Non-linearity

Although concentrations vary significantly from person to person, stable levels of maprotiline are directly proportional to the dose.

### Characteristics in patients

#### Elderly patients

The elderly patients may show higher plasma concentrations of maprotiline as a combined result of a decreased metabolism of the drug in elderly patients and a decreased renal function. In elderly patients (aged over 60 years), steady-state concentrations are higher than in younger patients on the same dosage; the apparent elimination half-life is longer, and the daily dose should be halved (see sections 4.2 and 4.8).

#### Renal Impairment

In renal impairment (creatinine clearance 24 to 37 mL/min), the elimination half-life and renal excretion of maprotiline are hardly affected, provided hepatic function is still normal. Renal excretion of metabolites is decreased, but this is compensated by increased elimination via the bile.

In patients with mild to moderate renal impairment and normal hepatic function may usually be treated with normal doses. Maprotiline is contraindicated in patients with severe renal impairment (see section 4.3).



# NEW ZEALAND DATA SHEET

## Hepatic impairment

Since the drug is primarily eliminated by metabolism, a significant impact on the clearance of the drug is anticipated in patients with hepatic failure. Maprotiline is contraindicated in patients with severe hepatic impairment (see section 4.3).

## Ethnic sensitivity

Although the impact of ethnic sensitivity and race on the pharmacokinetics of maprotiline has not been studied extensively, the metabolism of maprotiline is governed by genetic factors leading to poor and extensive metabolism of the drug.

## Slow or ultrafast metabolisers with respect to CYP2D6

In individuals with CYP2D6 slow metaboliser phenotype (5-10% of the Caucasian population) maprotiline exposure is expected to be ~ 250% higher than in individuals with fast metaboliser phenotype, giving them a stronger and more prolonged pharmacological effect.

Despite the lack of any reports on the pharmacokinetics of maprotiline and desmethylmaprotiline in individuals with ultrafast metaboliser phenotype, it is thought that the metabolism of maprotiline and desmethylmaprotiline will be accelerated in these individuals. The effect of Ludiomil® is probably reduced in these individuals and dose adjustment may be necessary.

## 5.3 Preclinical safety data

Preclinical data of Ludiomil®, based on conventional studies on the toxicity of repeated administration, genotoxicity, mutagenicity, carcinogenic potential for teratogenicity and reproductive toxicity, have shown no special hazard for humans.

Effects in preclinical studies were observed only at doses that were far beyond the maximum doses in humans and therefore have little relevance to clinical use.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Silica

Calcium phosphate

Lactose

Magnesium stearate

Stearic acid

Hydroxypropyl methylcellulose

Yellow iron oxide (E 172)

Polysorbate 80

Titanium dioxide (E 171)

Talc

Maize starch

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Red iron oxide (E 172)

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store below 30 °C.

### 6.5 Nature and contents of container

25 mg: Blister packs of 30, 50 and 100 tablets

75 mg: Blister packs of 20 and 30 tablets.

### 6.6 Special precautions for disposal

No special requirements

## 7 MEDICINE SCHEDULE

Prescription medicine

## 8 SPONSOR

AFT Pharmaceuticals Ltd.,  
PO Box 33.203  
Takapuna  
Auckland  
Email:customer.service@aftpharm.com

## 9 DATE OF FIRST APPROVAL

20/05/1982

## 10 DATE OF REVISION OF THE TEXT

November 2018

## SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
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## NEW ZEALAND DATA SHEET

November 2018	All	Reformat consistent with new Medsafe Data Sheet Template.
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