PACKAGE INSERT FOR DOMADOL

SCHEDULING STATUS:

S5

PROPRIETARY NAME (and dosage form):

DOMADOL (capsules)

COMPOSITION:

Each capsule contains tramadol hydrochloride 50 mg.

PHARMACOLOGICAL CLASSIFICATION:

A.2.9. Other analgesics

PHARMACOLOGICAL ACTION:

Tramadol hydrochloride is a centrally-acting synthetic opioid analgesic binding to specific opioid receptors. It is a non-selective, pure agonist at mu (μ), delta (δ) and kappa (κ) opioid receptors with a higher affinity for the μ receptor. Other mechanisms, which may contribute to its analgesic effect, are inhibition of neuronal re-uptake of noradrenaline and enhancement of serotonin release.

Tramadol hydrochloride does not promote histamine release.

Pharmacokinetics:

Tramadol hydrochloride is readily absorbed following oral administration. Oral bioavailability is approximately 68 % after a single dose and increases to 90 % at steady state. Onset of action is dose dependent but generally occurs within one hour of dosing, peaking within 2 to 3 hours. Duration of analgesia is about 6 hours. The rate or extent of absorption is not significantly affected by co-administration with food.

The bioavailability of tramadol hydrochloride after intramuscular injection or intravenous administration is the same; the mean peak serum concentration is achieved after 45 minutes.
Tramadol hydrochloride is primarily metabolised in the liver (90 %) with one of its metabolites, mono-*O*-desmethyltramadol (M1), being 2 to 4 times as potent as the parent compound.
Tramadol hydrochloride has a linear pharmacokinetic profile within the therapeutic dosage range.
Tramadol hydrochloride and its metabolites are excreted mainly in the urine. The elimination half-life is 5 to 7 hours, but is prolonged in impaired hepatic and renal function.
Tramadol hydrochloride crosses the blood-brain and placental barrier. Small amounts are excreted in breast milk unchanged or as the metabolite M1.

INDICATIONS:

DOMADOL is indicated for the management of moderate to moderately severe pain.

CONTRAINDICATIONS:

Hypersensitivity to tramadol hydrochloride or opioids.
Acute intoxication with alcohol, hypnotics, analgesic opioids or psychotropic medicines (due to the risk of respiratory depression).
Patients taking monoamine oxidase (MAO) inhibitors or within two weeks of their discontinuation (see **INTERACTIONS**).
Narcotic withdrawal treatment.
Respiratory depression especially in the presence of cyanosis and excessive bronchial secretions.
Increased intracranial pressure or central nervous depression due to head injury or cerebral disease.
Avoid the use of **DOMADOL** in patients with a history of addiction, as physical dependence of

Pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS:

the morphine-type may develop. Reinstatement of physical dependence in patients that have previously been dependent may occur with **DOMADOL.**

Use with caution in patients with a history of epilepsy or those susceptible to seizures (e.g. patients taking neuroleptics and other drugs that reduce the seizure threshold).

Use with caution in patients with renal or hepatic impairment and avoid if severe.

The administration of **DOMADOL** concurrently with other central nervous system medicines is likely to intensify and prolong CNS effects (see **INTERACTIONS**).

The possibility of respiratory depression cannot be excluded if the recommended dose is exceeded or other centrally depressant medicines are given concomitantly.

DOMADOL should not be used for the treatment of minor pain.

Patients should be warned not to operate machinery or drive a car while using **DOMADOL.**

INTERACTIONS:

Monoamine oxidase inhibitors (MAOIs): Because of its inhibitory effect on serotonin uptake, **DOMADOL** should not be used concomitantly with MAOIs or within 14 days after discontinuing such treatment (see **CONTRAINDICATIONS**).

Central nervous system (CNS) depression-producing medications, including alcohol and anaesthetics: Caution is recommended because concurrent use may potentiate the CNS depressant effects. The duration of anaesthesia may be prolonged when **DOMADOL** is combined with barbiturates.

Carbamazepine: Serum concentrations of **DOMADOL** are reduced by carbamazepine, resulting

in diminished analgesic activity of **DOMADOL**. Inhibitors of CYP3A4 such as ketoconazole and erythromycin may inhibit the metabolism of **DOMADOL**.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established. (See **CONTRAINDICATIONS**.)

DOSAGE AND DIRECTIONS FOR USE:

The dosage should be adjusted to the intensity of pain and the individual's response to the analgesic action of **DOMADOL**. **DOMADOL** should not be used for the treatment of minor pain.

Adults and children over the age of 14 years:

Oral administration:

Initial dose of 50 mg, followed by 100 mg twice daily.

The dose may be increased to 150 mg or 200 mg twice daily.

A total daily dose of 400 mg per day may not be exceeded.

For postoperative pain, administer 50 mg or 100 mg 4 to 6 hourly up to a total daily dose of 600 mg.

For less severe pain administer 50 mg or 100 mg 4 to 6 hourly.

Elderly:

The usual doses may be used except in patients 75 years of age and over. A downward adjustment of the dose and/or prolongation of the interval between doses are recommended.

Renal impairment:

The elimination of **DOMADOL** may be prolonged. The usual initial dose should be used, but for patients with creatinine clearance < 30 ml/min, the dosage interval should be increased to 12 hours.

The elimination of **DOMADOL** may be prolonged. The usual initial dose should be used but in

Hepatic impairment:

severe hepatic impairment, the dosage interval should be increased to 12 hours.

Duration of treatment:

Under no circumstances should **DOMADOL** be given for longer than absolutely necessary. If the nature and severity of the disease require long-term pain treatment with **DOMADOL** evaluation should be carried out initially and at regular intervals to assess efficacy, adverse events, and the need for further treatment.

SIDE EFFECTS:

Cardiovascular disorders:

Less frequent: Flushing, syncope, bradycardia, tachycardia, postural hypotension, cardiovascular collapse.

Neurological disorders:

More frequent: Fatigue, sedation, drowsiness, dizziness, headache.

Less frequent: Paraesthesia, amnesia, confusion, hallucinations, seizures (see **WARNINGS AND SPECIAL PRECAUTIONS**), syncope.

Gastrointestinal disorders:

More frequent: Nausea, vomiting, dry mouth, dyspepsia, constipation, diarrhoea, anorexia, abdominal pain.

Renal and urinary disorders:

Less frequent: Urinary retention, urinary frequency.

Hepato-biliary disorders:

Increase in liver enzymes.

Eye disorders:

Less frequent: Blurred vision.

Skin and subcutaneous tissue disorders:

More frequent: Sweating (especially when IV administration is too rapid), skin rashes, pruritus.

Less frequent: Vesicles, urticaria.

Other:

Angioedema, bronchospasm, anaphylaxis, and anaphylactoid reactions. These reactions may occur after the first dose. Toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdose:

(See **SIDE EFFECTS**.)

Symptoms of overdosage are typical of opioids, and include pinpoint pupils, slow heartbeat, slow or troubled breathing, weakness, seizures, cold, clammy skin.

Treatment of overdose:

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted. Treatment of restlessness is symptomatic and supportive.

Naloxone should be used to reverse some, but not all, symptoms caused by overdosage with **DOMADOL**. Administration of naloxone should be done with caution because it may precipitate seizures.

Diazepam has been found to be effective in treating convulsions caused by **DOMADOL** toxicity.

Haemodialysis is not recommended in overdose, since it removes less than 7 % of the

administered dose of **DOMADOL** in a 4-hour dialysis period.

IDENTIFICATION:

Size 2 hard gelatin capsule with red body and black cap with **DOMADOL** printed in white ink on cap and body, containing a white powder.

PRESENTATION:

Each carton contains 2, 3 or 10 x PVC/aluminium blister strips with 10 capsules each.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

37/2.9/0596

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Unichem SA (Pty) Ltd

1st Floor, Pinewood Park

Lonsdale Road, Pinelands

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

29/07/2005