Professional Information for DOMADOL PLUS

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DOMADOL PLUS film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 37,5 mg tramadol hydrochloride and 325 mg paracetamol.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Yellow, capsule shaped, biconvex, film-coated tablet, plain on one side and a break line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOMADOL PLUS is indicated for the management of moderate to moderately-severe pain in adults.

DOMADOL PLUS is not recommended for minor pain that may be treated adequately through lesser means.

4.2 Posology and method of administration

Posology

To be used in adults and children over 16 years of age.

DO NOT EXCEED THE RECOMMENDED DOSE.

Adults

For the management of pain, the recommended dose of DOMADOL PLUS is 1 or 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

A titration period of several days with gradual dose increases at the initiation of DOMADOL PLUS therapy, may be beneficial for some patients. The tolerability of tramadol can be improved by starting tramadol at a low dose with gradual upward dose titration to reach doses that provide sufficient pain relief.

Special populations

Renal impairment

For patients with creatinine clearance < 30 mL/min, the dosing interval of DOMADOL PLUS should be increased not to exceed 2 tablets every to 12 hours.

4.3 Contraindications

- Hypersensitivity to tramadol hydrochloride, paracetamol, other opioids such as codeine or to any of the excipients listed in section 6.1.
- Severe liver function impairment.
- Acute intoxication with alcohol, hypnotic medicines, centrally acting analgesic medicines, opioids or psychotropic medicines.
- Patients who are receiving monoamine oxidase inhibitors (MAOIs) or within two weeks of their withdrawal (see sections 4.4 and 4.5).
- Use during narcotic withdrawal treatment.
- Patients with respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
- Patients with increased intracranial pressure or central nervous system depression, due to head injury or cerebral disease.
- Epilepsy not controlled by treatment (see section 4.4).

4.4 Special warnings and precautions for use

DOMADOL PLUS contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or poison centre must be contacted immediately.

The maximum dose of 8 tablets of DOMADOL PLUS should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing medicines concurrently without the advice of a health care provider.

In severe renal insufficiency (creatinine clearance < 10 mL/mm), DOMADOL PLUS is not recommended.
DOMADOL PLUS should be used with caution in patients with impaired renal function and in patients prone to convulsive disorders or in shock.

In patients with severe hepatic impairment DOMADOL PLUS should not be used (see section 4.3). The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease. In moderate cases, prolongation of dosage interval should be carefully considered.
In severe respiratory insufficiency, DOMADOL PLUS is not recommended.

Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.

Convulsions

Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medicines that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia.

The risk of seizures may also be increased in patients with epilepsy, with a history of seizures or in patients with recognised risk for seizures (e.g. medicine and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramadol overdose).
Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceeding the recommended upper dose limit.
Patients known to suffer from cerebral convulsions should be carefully monitored during treatment with tramadol.

Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5).

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

CYP2D6 ultra-rapid metabolism of tramadol

Patients who are CYP2D6 ultra-rapid metabolisers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. This rapid conversion may lead to higher than expected serum M1 levels which could lead to an increased risk of respiratory depression. In these patients the following is recommended:

- alternative medicine
- dose reduction
- increased monitoring for signs of tramadol overdose, such as respiratory depression.

Medicine abuse and dependence

Tolerance and physical and/or psychological dependence may develop, even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly (see section 4.2).
Tramadol has been associated with craving, medicine-seeking behaviour and tolerance development.
Cases of tramadol abuse and dependence have been reported.
Tramadol should not be used in opioid-dependent patients, since it can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids.

Paracetamol in overdosage may cause hepatic toxicity. DOMADOL PLUS, should only be taken under medical supervision by patients suffering from liver or kidney disease.
Abrupt discontinuation of DOMADOL PLUS may lead to withdrawal symptoms. Panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual central nervous system (CNS) symptoms have been reported with abrupt discontinuation of tramadol. Withdrawal symptoms may be avoided by tapering it at the time of discontinuation.
Cases of dependence and abuse have been reported (see section 4.8).

A study has shown that the use of tramadol during general anaesthesia with enflurane and nitrous oxide enhanced the intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

Serious skin reactions

There have been reports of serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients receiving paracetamol. Patients should be informed about the signs of serious skin reactions and the use of DOMADOL PLUS should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

CNS depressants

Co-administration of DOMADOL PLUS with CNS depressants such as alcohol, opioids, anaesthetics, phenothiazines, tranquilisers or sedative hypnotics is likely to intensify and prolong CNS effects. DOMADOL PLUS should not be taken with alcohol containing beverages (see section 4.5).

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines

Concomitant use of DOMADOL PLUS and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe DOMADOL PLUS concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of the concomitant treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Hyponatraemia

Hyponatraemia has been reported with the use of DOMADOL PLUS, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medicines that may cause hyponatraemia.

This hyponatraemia appeared to be the result of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion and resolved with discontinuation of DOMADOL PLUS and appropriate treatment (e.g. fluid restriction).

Therefore, it is recommended to monitor patients with predisposing risk factors for signs and symptoms of hyponatraemia during DOMADOL PLUS treatment.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use is contraindicated with:

Non-selective monoamine oxidase inhibitors (MAOIs)

Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

Selective-A MAOIs

Extrapolation from non-selective MAOIs.

Risk of serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

Selective-B MAOIs

Central excitation symptoms evocative of a serotonergic syndrome:

diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even

coma.

In patients that have received recent treatment with MAOIs, a delay of two weeks should occur before treatment with DOMADOL PLUS, as the potentiation of serotonergic and noradrenergic effects may result.

Concomitant use is not recommended with:

Alcohol

Alcohol increases the sedative effect of opioid analgesics. The effect on alertness can make driving of vehicles and the use of machines dangerous. The concomitant intake of alcoholic drinks and of medicines containing alcohol should be avoided (see section 4.4).

Carbamazepine and other enzyme inducers

Concomitant administration of DOMADOL PLUS and carbamazepine may cause significantly decreased tramadol and M1 concentrations. Patients receiving carbamazepine and other enzyme

inducers may have a significantly reduced analgesic effect from the tramadol component of DOMADOL PLUS.

Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)

Concomitant administration with opioid agonists-antagonists may cause a decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

Concomitant use which needs to be taken into consideration:

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and seizure threshold-lowering medicines (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants and
mirtazapine may cause serotonin toxicity.
Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus.
- Inducible or ocular clonus with agitation or diaphoresis.
- Tremor and hyperreflexia.
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Other opioid derivatives (including antitussive medicines and substitutive treatments), benzodiazepines and barbiturates increased the risk of respiratory depression which can be fatal in cases of overdose.

Other central nervous system depressants, such as other opioid derivatives (including antitussive medicines and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive medicines, thalidomide and baclofen can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

Sedating medicines such as benzodiazepines or related substances: The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effects. The dose and duration of the concomitant use should be limited (see section 4.4).

Concomitant administration with CYP2D6 inhibitors such as fluoxetine, paroxetine, quinidine and amitriptyline could result in some inhibition of tramadol metabolism.

Concomitant administration of diflunisal and paracetamol produced a 50 % increase in paracetamol plasma levels in normal volunteers. DOMADOL PLUS should be used cautiously and patients should be monitored carefully.

Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and rare alterations of warfarin effect, including elevation of prothrombin times.

There have been reports of increased prothrombin time/international normalised ratio (INR) in some patients receiving warfarin-like compounds concurrently with DOMADOL PLUS. Therefore, periodic evaluation of prothrombin time/INR should be performed when DOMADOL PLUS is administered concurrently with warfarin like compounds.

The pre- or postoperative application of the antiemetic 5-HT_3 antagonist, ondansetron increased the requirement of tramadol in patients with postoperative pain.

Simultaneous administration with cimetidine is associated with clinically insignificant changes in serum concentrations of tramadol. Therefore, no alteration of the DOMADOL PLUS dosage regimen is recommended for patients receiving chronic cimetidine therapy.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Since DOMADOL PLUS is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

Paracetamol

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages.

Tramadol hydrochloride

Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol in pregnant women.

Breastfeeding

Since DOMADOL PLUS is a fixed combination of active ingredients including tramadol, it should not be ingested during breastfeeding.

Paracetamol

Paracetamol is excreted in breastmilk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding by women using single ingredient medicines containing only paracetamol.

Tramadol hydrochloride

Approximately 0,1 % of the maternal dose of tramadol is excreted in breastmilk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breastfed infants of 3 % of the maternal weight-adjusted dosage. For this reason, tramadol should not be used during lactation or alternatively, breastfeeding should be discontinued during treatment with tramadol.

Fertility

Tramadol hydrochloride

Post-marketing surveillance does not suggest an effect of tramadol on fertility.

Animal studies did not show an effect of tramadol on fertility.

Tramadol hydrochloride / paracetamol

No study on fertility was accomplished with the combination of tramadol and paracetamol.

4.7 Effects on ability to drive and use machines

DOMADOL PLUS may cause side effects, such as drowsiness or dizziness, which may be enhanced in conjunction with alcohol or other CNS depressants. Caution is advised before driving a vehicle or operating machinery until the effects of DOMADOL PLUS are known.

4.8 Undesirable effects

Blood and lymphatic system disorders

Less frequent: anaemia

Metabolism and nutrition disorders

Less frequent: decreased body mass

Frequency unknown: hypoglycaemia

Psychiatric disorders

Frequent: confusional state, altered mood, anxiety, nervousness, euphoric mood, sleep disorders, anorexia, insomnia

Less frequent: depression, hallucinations, nightmares, delirium, medicine dependence, amnesia, depersonalisation, emotional lability, impotence, abnormal thinking

Nervous system disorders

Frequent: dizziness, somnolence, headache, trembling

Less frequent: involuntary muscular contractions, paraesthesia, ataxia, convulsions, syncope, speech disorders, hypertonia, migraine, aggravated migraine, stupor, vertigo

Eye disorders

Less frequent: blurred vision, miosis, mydriasis, abnormal vision

Ear and labyrinth disorders

Less frequent: tinnitus

Cardiac disorders

Less frequent: palpitations, tachycardia, dysrhythmia

Vascular disorders

Frequent: hot flushes

Less frequent: hypertension, aggravated hypertension, hypotension

Respiratory, thoracic and mediastinal disorders

Less frequent: dyspnoea

Gastrointestinal disorders

Frequent: nausea, vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence

Less frequent: dysphagia, melaena, tongue oedema

Skin and subcutaneous tissue disorders

Frequent: increased sweating, pruritus, rash

Less frequent: urticaria

Renal and urinary disorders

Less frequent: albuminuria, micturition disorder (dysuria and urinary retention), oliguria

General disorders and administration site conditions

Frequent: asthenia, fatigue

Less frequent: chills, chest pain, rigors, withdrawal syndrome

Investigations

Less frequent: increased transaminases.

Post-marketing experience

Although not observed during clinical trials, the occurrence of the following undesirable effects known to be related to the administration of tramadol or paracetamol cannot be excluded:

Tramadol hydrochloride

Orthostatic hypotension, allergic reactions with respiratory symptoms (e.g. bronchospasm, wheezing, angioneurotic oedema), including anaphylaxis and urticaria, Stevens Johnson syndrome/TENS, cognitive dysfunction, suicidal tendency and hepatitis, elevated creatinine levels.

Serotonin syndrome (symptoms may include fever, excitation, shivering and agitation) when used concomitantly with other serotonergic medicines such as SSRIs and MAOIs, movement disorder, alterations of warfarin effect (including elevation of prothrombin times), hypoglycaemia, hyponatraemia and/or SIADH (usually in patients with predisposing risk factors, such as the elderly or those using concomitant medicines that may cause hyponatraemia), bradycardia, changes in appetite, motor weakness, respiratory depression, mood changes (usually euphoric mood and occasionally dysphoria), changes in activity (usually suppression, but occasionally an increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders), worsening of asthma.

Paracetamol

Allergic reactions (primarily skin rash), hypersensitivity secondary to paracetamol (generally controlled by discontinuation of the medicine, and when necessary, symptomatic treatment), blood dyscrasias (including thrombocytopenia and agranulocytosis), hypoprothrombinaemia (when administered with warfarin like compounds).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DOMADOL PLUS is important. It allows continued monitoring of the benefit/risk balance of DOMADOL PLUS. Health care professionals are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The clinical presentation of overdosage may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both.

Tramadol hydrochloride

Symptoms

In principle, on intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular, miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Treatment

Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should
be used to reverse respiratory depression; fits can be controlled with
diazepam.
Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Treatment of acute intoxication with DOMADOL PLUS with haemodialysis or haemofiltration alone, is therefore not suitable for detoxification.

Paracetamol

Prompt treatment is essential. In the event of an overdosage, consult a doctor immediately, or take the person to a hospital directly. A delay in starting treatment may mean that antidote is given too late to be effective.
Evidence of liver damage is often delayed until after the time for effective treatment has lapsed. Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 – 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours include pallor,
nausea, vomiting, anorexia and possibly abdominal pain. Mild symptoms during the first two days of

acute poisoning do not reflect the potential seriousness of the overdosage.

Liver damage may become apparent 12 to 48 hours or later after ingestion, initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may lead to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. Cardiac dysrhythmias have been reported.

Liver damage is possible in adults who have taken 7,5 – 10 g or more of paracetamol. It is considered that excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

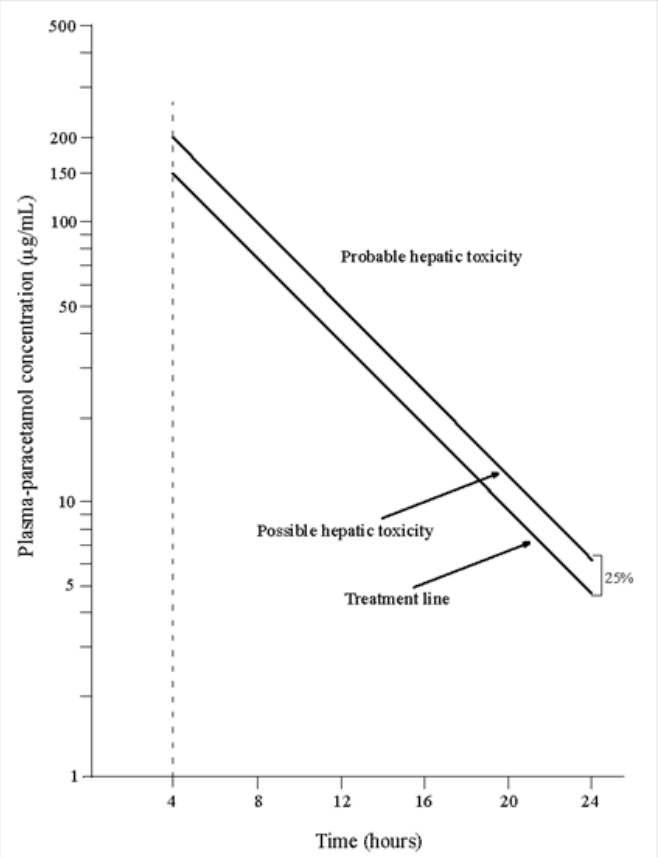
Treatment

***N*-acetylcysteine** should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of overdosage. Treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

An initial dose of 150 mg/kg *N*-acetylcysteine in 200 mL dextrose injection given intravenously over 15 minutes, followed by an infusion of 50 mg/kg in 500 mL dextrose injection over the next four hours, and then 100 mg/kg in 1 000 mL dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children.**

Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water may be administered initially, followed by 70 mg/kg every four hours for seventeen doses.

A plasma paracetamol level should be determined four hours after ingestion in all cases of suspected overdosage. Levels done before four hours, unless high may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with *N*-acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below. The nomogram should be used only in relation to a single acute ingestion.



Source: Martindale, The Complete Drug Reference, Acetaminophen, Online Edition, 2nd Quarter 2020.

Those whose plasma paracetamol levels are above the “normal treatment line", should continue *N*-acetylcysteine treatment with 100 mg/kg IV over sixteen hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “treatment line". Prothrombin index correlates best with survival.

Monitor all patients with significant ingestions for at least ninety six hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Opioids in combination with non-opioid analgesics; tramadol and paracetamol.

ATC code: N02AJ13.

Tramadol hydrochloride

Tramadol is an opioid analgesic that acts on the CNS. Tramadol is a pure non-selective agonist of the μ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect.

Paracetamol

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

5.2 Pharmacokinetic properties

Absorption

Tramadol hydrochloride

Racemic tramadol is rapidly and almost completely absorbed after oral administration reaching peak activity in 2 to 3 hours. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %.

Tramadol hydrochloride / paracetamol

After administration of tramadol hydrochloride/paracetamol, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol. The oral administration of tramadol hydrochloride/paracetamol with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that tramadol hydrochloride/paracetamol can be taken independently of meal times.

Distribution

Tramadol hydrochloride

Tramadol has a high tissue affinity ($V_{d,\beta}$ = 203 ± 40 L). It has a plasma protein binding of about 20 %.

Paracetamol

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0,9 L/kg. A relative small portion (~20 %) of paracetamol is bound to plasma proteins.

Biotransformation

Tramadol

Tramadol is extensively metabolised after oral administration.

Tramadol is metabolised through *O*-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through *N*-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through *N*-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent medicine. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing.

Paracetamol

Paracetamol is principally metabolised in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4 %) is metabolised by cytochrome P450 to an active intermediate (the *N*-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid.
However, during massive overdose, the quantity of this metabolite is increased.

Elimination

Tramadol and its metabolites are eliminated mainly by the kidneys. About 30 % of the dose is excreted in urine as unchanged medicine, whereas 60 % of the dose is excreted as metabolites. The half-life of

paracetamol is approximately 2 to 3 hours in adults, and shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9 % of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients for DOMADOL PLUS:

Colloidal anhydrous silica

Magnesium stearate (E572)

Maize starch

Microcrystalline cellulose (E460(i))

Povidone

Sodium starch glycolate

Talcum.

Film coating for DOMADOL PLUS:

Opadry Yellow containing:

Hypromellose (E464)

Iron oxide yellow (colourant) (E172)

Polyethylene glycol (E1521)

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Store at or below 30 °C.

6.4 Special precautions for storage

Protect from light and moisture.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Transparent, clear, PVC/PVdC aluminium blister strip containing 10 tablets packed in an outer carton.

Pack sizes: 30 or 60 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico, Ground Floor, Unit 4,

10 Church Street, Durbanville,

Cape Town

7551

8. REGISTRATION NUMBER

DOMADOL PLUS: 54/2.9/0185

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 20 February 2024

10. DATE OF REVISION OF THE TEXT

20 February 2024