PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 5

1 NAME OF THE MEDICINE

ULTRACET Film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light yellow, film-coated capsule-shaped tablet engraved “J-C” on one side and “T/P” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ULTRACET 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.

For the management of pain, the recommended maximum single dose of ULTRACET is 1 or 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. The lowest effective dose should be used for the shortest period of time.

A titration period of several days with gradual dose increases at the initiation of ULTRACET therapy may be beneficial for some patients. Clinical studies with tramadol in patients with moderate to moderately severe chronic pain indicate that 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

Children below 16 years of age

The use of ULTRACET is contraindicated in children below 12 years of age (see section 4.3, Contraindications).

The safety and effectiveness of ULTRACET in children aged 12 to below 16 years of age has not been established (see section 4.3, Contraindications and section 4.4, Special warnings and precautions for use - Other risk factors for life-threatening respiratory depression in children).

Elderly (65 years of age and older)

No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥ 65 years of age and younger subjects.

Renal impairment:

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

Hepatic impairment

The use of ULTRACET in patients with moderate to severe hepatic impairment is contraindicated.

Method of administration

ULTRACET are for oral administration.

Tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

ULTRACET can be administered without regard to food.

4.3 Contraindications

- ULTRACET is contraindicated in patients with a known hypersensitivity to tramadol, paracetamol, other opioids such as codeine or to any of the excipients listed in section 6.1
- It is also contraindicated in cases of acute intoxication with alcohol, hypnotics, other opioids or psychotropic medicines.
- Moderate to severe hepatic impairment.
- It should not be administered to patients who are receiving monoamine oxidase (MAO) inhibitors or within two weeks of their withdrawal.

- ULTRACET must not be used for treatment of narcotic withdrawal

- ULTRACET should not be given to patients with respiratory depression

- ULTRACET should not be given to patients with head injury or cerebral disease, with or without increased intracranial pressure or central nervous system depression due to head injury or cerebral disease.

- ULTRACET can cause seizures (convulsions), hence it should not be used in patients with epilepsy or seizures of any cause (see section 4.4)

- ULTRACET is contraindicated in all children younger than 12 years of age.

- ULTRACET is contraindicated in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.

4.4 Special warnings and precautions for use

This product 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.

Dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should only take paracetamol containing products under medical supervision.

Seizures

ULTRACET should not be used in patients with a history of epilepsy or those susceptible

to seizures (See section 4.3). Seizures have been reported in patients receiving ULTRACET at dosages within the recommended dosage range. The risk of seizures is enhanced in patients exceeding the recommended dose, or in patients concomitantly taking tricyclic anti-depressants or other tricyclic compounds e.g. selective serotonin re-uptake inhibitors (SSRI, antidepressants or anorectics), MAO-inhibitors, opioids, other medicines that reduce the seizure threshold and neuroleptics.

The risk of seizures may also be increased in patients with epilepsy, those with a history of seizures or in patients with a recognised risk for seizures e.g. drug and alcohol withdrawal, intracranial infections, head trauma, metabolic disorders and naloxone administration with tramadol overdose.

Anaphylactic reactions

Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET.

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol.

Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

Respiratory depression

Opioids can cause sleep-related breathing disorders such as sleep apnoea syndromes (including central sleep apnoea [CSA]) and hypoxia (including sleep-related hypoxia) (see section 4.8, Undesirable reactions). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep

apnoea or a worsening of an existing sleep apnoea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see section 4.4, Special warnings and precautions for use – Withdrawal).

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 result in higher than expected serum M1 levels which could lead to an increased risk of respiratory depression (see section 4.9, Overdose - *Tramadol: symptoms and signs*). Alternative medication, dose reduction and/or increased monitoring for signs of tramadol toxicity, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolisers.

Even at labeled dosage regimens, individuals who are ultra-rapid metabolisers may have life-threatening or fatal respiratory depression or experience signs of toxicity such as extreme sleepiness, confusion, or shallow breathing (see section 4.9, Overdose - *Tramadol: symptoms and signs).*

Other risk factors for life-threatening respiratory depression in children

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Based upon post marketing reports with tramadol, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol (see section 4.3, Contraindications). Furthermore, children with obstructive sleep apnoea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect (see section 4.3, Contraindications). Because of the risk of life-

threatening respiratory depression and death, avoid the use of ULTRACET in adolescents younger than 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnoea and concomitant use of other medicines that cause respiratory depression.

As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and signs of opioid overdose (see section 4.2, Posology and section 4.9, Overdose-Symptoms and signs, Tramadol).

Use with Central Nervous System (CNS) depressants, including alcohol

The concomitant use of tramadol with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression. ULTRACET should be used with caution and in reduced dosages when administered to patients receiving CNS depressants (see section 4.5, Interactions with other medicines and other forms of interaction).

Drug dependence and potential for abuse

ULTRACET has a dependence potential and tolerance, psychic and physical dependence of the morphine-type (μ opioid) may develop with its use. The medicine has been associated with craving drug-seeking behaviour and tolerance development. Cases of abuse and dependence on ULTRACET have been reported.

ULTRACET should not be used in opioid-dependent patients. ULTRACET can reinstate physical dependence in patients that have been previously dependent or chronically using other opioids. In patients with a tendency to drug abuse, a history of drug dependence or

who are chronically using opioids, treatment with ULTRACET is not recommended. ULTRACET should not be given to patients who are suicidal or prone to addiction.

Increased risk of hepatotoxicity with alcohol use

Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use.

Withdrawal

Withdrawal symptoms may occur if ULTRACET is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus, and unusual CNS symptoms have also been reported with abrupt discontinuation of ULTRACET. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication dosages.

Use with serotonergic medicines

Use ULTRACET with great caution in patients taking serotonergic medicines including SSRIs. Concomitant use of tramadol with serotonergic medicines including SSRI's increases the risk of adverse events, including seizure and serotonin syndrome (see section 4.5, Interaction with other medicines and other forms of interaction).

Renal Impairment

ULTRACET has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of ULTRACET be increased not to exceed 2 tablets every 12 hours.

Serious skin reactions

Serious skin reactions such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported in patients receiving paracetamol. Patients should be informed about the signs of

serious skin reactions and use of ULTRACET should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hyponatraemia

Hyponatraemia has been reported with the use of ULTRACET, 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 secretion (SIADH) and resolved with discontinuation of ULTRACET and appropriate treatment (e.g. fluid restriction). During ULTRACET treatment, monitoring for signs and symptoms of hyponatraemia is recommended for patients with predisposing risk factors.

Precautions – general:

The recommended dose of ULTRACET should not be exceeded.

Do not co-administer ULTRACET with other tramadol or paracetamol containing products.

4.5 Interaction with other medicines and other forms of interaction

Table 1: Drug interaction with ULTRACET

Inhibitors of CYP2D6	
Mechanism	Enzyme inhibition in decreased rate of metabolism of tramadol
Clinical impact	The concomitant use of ULTRACET and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of ULTRACET is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may

	result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. After stopping an inhibitor of CYP2D6, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, and may cause potentially fatal respiratory depression.
Intervention	If concomitant use of an inhibitor of CYP2D6 is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome (see section 4.4, Special warnings and precautions for use- CYP2D6 ultra rapid metabolism of tramadol) If an inhibitor of CYP2D6 is discontinued, consider lowering ULTRACET dosage until stable medicine effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
Examples	Quinidine, fluoxetine, paroxetine, amitriptyline and bupropion
Inhibitors of CYP3A4	
Mechanism	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
Clinical impact	The concomitant use of ULTRACET and an inhibitor of CYP3A4 can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. After stopping an inhibitor of CYP3A4, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease, resulting in decreased opioid

	efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.
Intervention	If concomitant use is necessary, consider dosage reduction of ULTRACET until stable medicine effects are achieved. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of ULTRACET is achieved. If an inhibitor of CYP3A4 is discontinued, consider increasing the ULTRACET dosage until stable medicine effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
Examples	Macrolide antibiotics (e.g. erythromycin), azole-antifungal medicines (e.g. ketoconazole), protease inhibitors (e.g. ritonavir)
CYP3A4 Inducers	
Mechanism	Enzyme induction resulting in increased rate of metabolism of tramadol
Clinical impa	The concomitant use of ULTRACET and an inducer of CYP3A4 can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol. After stopping an inducer of CYP3A4, as the effects of the inducer decline, the tramadol plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.
Intervention	If concomitant use is necessary, consider increasing the ULTRACET dosage until stable medicine effects are achieved. Follow patients for signs of opioid withdrawal.

	If an inducer of CYP3A4 is discontinued, consider ULTRACET dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. Patients taking carbamazepine, an inducer of CYP3A4, may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because the seizure risk associated with tramadol, concomitant administration of ULTRACET and carbamazepine is not recommended.
Examples	Rifampin, carbamazepine, phenytoin
Benzodiazepines and other central nervous system (CNS) depressants including alcohol	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical impact	The concomitant use of tramadol with central nervous system depressants, such as benzodiazepines and other sedatives/hypnotics, anaesthetic medicines, phenothiazines, tranquilisers, opioids or alcohol, may produce additive CNS depressant effects, such as profound sedation and respiratory depression. If concomitant use of ULTRACET with a CNS depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both medicines, and follow patients closely for sign of respiratory depression. Due to additive pharmacodynamic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma and death.
Intervention	Reserve concomitant prescribing of these medicines for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of

	respiratory depression and sedation (see section 4.4, Special warnings and precautions for use).
Examples	Benzodiazepines and other sedatives/hypnotics, tranquilisers, muscle relaxants, general anaesthetics, other opioids, alcohol.
Serotonergic Medicines	
Mechanism	Additive or synergistic pharmacodynamic effect
Clinical impact	Concomitant use of tramadol with serotonergic medicines increases the risk of adverse events, including seizures and serotonin syndrome.
Intervention	Use caution when administering ULTRACET in patients taking serotonergic medicines and monitor for signs of adverse events. Discontinue ULTRACET if serotonin syndrome is suspected.
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonist, medicines that affect the serotonin neurotransmitter system (e.g. mirtazapine and trazodone) and some muscle relaxants (e.g. cyclobenzaprine, metaxalone).
Monoamine Oxidase Inhibitors (MAOIs)	
Mechanism	Additive or synergistic pharmacodynamic effects
Clinical impa	The concomitant use of ULTRACET with MAOIS, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see section 4.3, Contraindications). MAOI interactions with opioids may manifest as serotonin syndrome (see section 4.4, Special warnings and precautions for use – Use with serotonin reuptake inhibitors) or opioid toxicity (e.g. respiratory depression, coma) (see section 4.4, Special warnings and precautions for use – Respiratory depression).

Intervention	Do not use ULTRACET in patients taking MAOIs or within 14 days of stopping such treatment.
Examples	Phenelzine, tranylcypromine, linezolid
Warfarin	
Clinical impa	As medically appropriate, periodic evaluation of prothrombin time should be performed when ULTRACET and these medicines are administered concurrently due to reports of increased International Normalized Ratio (INR) in some patients. Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times. Paracetamol may produce hypoprothrombinaemia when administered with warfarin-like medicines.
Intervention	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.
Cimetidine	
Clinical impact	Concomitant administration of tramadol with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safe use in pregnancy has not been established.

ULTRACET is not recommended for pregnant mothers because tramadol has been shown to cross the placenta and appears in breast milk.

The use of opioids during childbirth might result in respiratory depression in the newborn infant.

Prolonged use of ULTRACET, or other opioids, during pregnancy may lead to neonatal opioid withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.

Lactation

Safe use in lactation has not been established.

ULTRACET is not recommended for lactating mothers because tramadol appears in breast milk.

4.7 Effects on ability to drive and use machines

ULTRACET may affect mental or physical abilities to the extent that the ability to drive and operate machinery may be impaired.

4.8 Undesirable effects

ULTRACET tablets may have side effects. These are classified as follows:

- very common (≥ 1/10)
- common (≥ 1/100, < 1/10)
- uncommon (≥ 1/1 000, < 1/100)
- rare (≥ 1/10 000, < 1/1 000)
- very rare (< 1/10 000) including isolated reports

The most frequently reported side effects were of the gastrointestinal and central nervous systems.

Table 2: Adverse reactions identified during clinical trials with ULTRACET

SYSTEM ORGAN CLASS	Very common (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1 000, < 1/100)
Skin and appendages disorders		Pruritus, rash, increased sweating	
Central and peripheral nervous system	Dizziness, somnolence	Headache, tremor	Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo
Vision disorders			Abnormal vision
Hearing and vestibular disorders			Tinnitus
Psychiatric disorders		Anorexia, anxiety, confusion, euphoria, insomnia, nervousness	Amnesia, depersonalisation, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, abnormal thinking
Gastrointestinal disorders	Nausea	Abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, dry mouth, vomiting	Dysphagia, melaena, tongue oedema
Liver and biliary system disorders			Liver test abnormalities, hepatitis
Metabolic and nutritional disorders			Weight decrease

Cardiovascular disorders, general			Hypertension, aggravated hypertension, hypotension
Heart rate and rhythm disorders			Dysrhythmia, palpitation, tachycardia
Respiratory system disorders			Dyspnoea
Red blood cell disorders			Anaemia
Urinary system disorders			Albuminuria, micturition disorder, oliguria, urinary retention
Body as a whole – general disorders		Asthenia, fatigue, hot flushes	Chest pain, rigors, syncope, withdrawal syndrome

Agranulocytosis, leucopaenia, neutropaenia, pancytopaenia, thrombocytopaenia are rare and usually mild side effects experienced with paracetamol.

Table 3: Adverse reactions identified during post marketing experience with ULTRACET

System organ class	**Adverse reaction**
Metabolism and nutrition disorders	Hyponatraemia/syndrome of inappropriate antidiuretic hormone
Immune system disorders	Fixed eruption

Other clinically significant adverse experiences previously reported in clinical trials or post marketing reports with tramadol hydrochloride include:

Vasodilation, orthostatic hypotension, myocardial ischaemia, pulmonary oedema, allergic reactions (including anaphylaxis and urticaria, Stevens Johnson Syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis liver failure and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine.

Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic medicines such as SSRIs and MAO inhibitors. Post marketing experience with the use of tramadol containing medicines included reports of delirium, miosis, mydriasis, and speech disorder, and reports of movement disorder. Post marketing surveillance of tramadol has revealed alterations of warfarin effect, including elevation of prothrombin times. Cases of hypoglycaemia have been reported.

Cases of hyponatraemia and/or SIADH have been reported in patients taking tramadol, usually in patients with predisposing risk factors, such as the elderly or those using concomitant medicines that may cause hyponatraemia.

Other clinically significant adverse experiences previously reported in clinical trials or post marketing reports with paracetamol include:

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to paracetamol are rare and generally controlled by discontinuation of ULTRACET, and when necessary, symptomatic treatment. There have been several reports that suggest that paracetamol may produce hypoprothrombinaemia when administered with warfarin like compounds. In other studies, prothrombin time did not change.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked

to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Accidental ingestion

Accidental ingestion of tramadol can result in respiratory depression and seizures due to an overdose with tramadol. Respiratory depression and seizures have been reported in a child following ingestion of a single tablet.

Fatalities due to tramadol overdose have also been reported.

Signs and Symptoms

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

Tramadol

The symptoms of tramadol overdosage may include miosis, vomiting, fast heartbeat, consciousness disorders up to coma, cardiovascular collapse, cardiac arrest, death, respiratory depression and/or seizures. In addition, cases of QT prolongation have been reported during overdose.

Paracetamol

Symptoms of paracetamol overdosage in the first 24 hours include gastrointestinal abnormality, pallor, nausea, vomiting, malaise, anorexia and diaphoresis. Mild symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage.

Paracetamol in massive overdosage may cause hepatic toxicity. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment

Tramadol

A single or multiple overdose with ULTRACET may be a potentially lethal polymedication overdose, and appropriate expert consultation, if available, is recommended.

While naloxone will reverse some, but not all symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Based on experience with tramadol, haemodialysis is not expected to be helpful in an overdose because it removes less than 7 % of the administered dose in a 4-hour dialysis period.

Primary attention should be given to maintaining adequate ventilation and circulatory functions along with general supportive treatment.

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 the 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.

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 / increased INR. 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.

Treatment for paracetamol overdosage:

It is recommended that any adult person who has ingested 5 - 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding four hours, should have the stomach emptied by lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose endotracheal intubation should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible preferably within eight hours of overdosage. Administration should not be delayed while awaiting the results of the plasma assay. 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 1000 mL dextrose injection over the next sixteen hours. **The volume of intravenous fluid should be modified for children**. Sodium chloride 0,9 % injection may be used where dextrose 5 % injection is unsuitable.

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 at 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 nomogram should be used after ingestion of ULTRACET.

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: N02A J 13

Pharmacodynamic effects

Tramadol is a centrally acting analgesic that acts by stimulation of μ-opioid receptors as well as by a weak inhibition of the re-uptake of norepinephrine (noradrenaline) and serotonin. Paracetamol also has centrally acting analgesic effects.

5.2 Pharmacokinetic studies

Absorption

Tramadol is well absorbed after oral administration, reaching peak activity in 2 to 3 hours. The mean absolute bioavailability of a single 100 mg oral dose is approximately 75 %, increasing to approximately 90 % with multiple dosing. Oral absorption of paracetamol following administration of tramadol/paracetamol tablets gives a peak plasma concentration of paracetamol within one hour and is not affected by co-administration with tramadol.

Metabolism

Tramadol and paracetamol are both extensively metabolised in the liver. Tramadol is metabolised by a number of pathways including the cytochrome P450 isoenzymes, CYP 3A4 and CYP2D6 as well as by conjugation. Paracetamol is metabolised from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner.

Elimination

Approximately 30 % of tramadol is excreted unchanged in the urine. Tramadol and its metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of tramadol and its M1 metabolite are approximately 6 and 7 hours respectively. The half-life of paracetamol is about 2-3 hours in adults. Less than 9 % of paracetamol is excreted unchanged in the urine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carnauba wax

Hypromellose

Iron oxide

Magnesium stearate

Maize starch

Polyethylene glycol

Polysorbate 80

Powdered cellulose

Pregelantised starch

Sodium starch glycolate

Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a cool, dry place at or below 30 ^{0}C. Do not remove the blisters from the carton until required.

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store ULTRACET securely, in a location not accessible by others.

6.5 Nature and contents of container

Clear colourless PVC blister packs of 60 tablets. The blisters are packed in cartons containing 6 strips of 10 tablets each.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused ULTRACET should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty) Ltd

(Reg. No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand, 1685

Tel: +27 (0) 11 518 7000

RA-JACZA-MedInfo@its.jnj.com

8 REGISTRATION NUMBER

ULTRACET: 44/2.9/0931

9 DATE OF FIRST AUTHORISATION

Date of registration for ULTRACET: 15 August 2013

10 DATE OF REVISION OF TEXT

Date of the most recently revised Professional Information

Insert as approved by the Advisory Clinical Committee:

01 September 2022