**SUMMARY OF PRODUCT & CHARACTERISATION**
**METADOL FIZZ**
(Paracetamol 325 mg & Tramadol Hydrochloride 37.5 mg Effervescent Tablet)

## 1. Name of the medicinal product
**METADOL FIZZ**
(Paracetamol 325 mg & Tramadol Hydrochloride 37.5 mg Effervescent Tablet)

## 2. Qualitative and quantitative composition
Each Effervescent Tablet contains:
Paracetamol BP …….. 325 mg
Tramadol Hydrochloride BP……37.5 mg
Excipients ……... Q.S .

## 3. Pharmaceutical form:
Tablet

## 4. Clinical particulars
### 4.1 Therapeutic indications
Metadol fizz is indicated for the symptomatic treatment of moderate to severe pain.

The use of Metadol fizz should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol hydrochloride and paracetamol (see also section 5.1).

### 4.2 Posology and method of administration
*Posology*

The use of Metadol fizz should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol hydrochloride and paracetamol.

The dose should be adjusted to intensity of pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected. The total dose of 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day should not be exceeded. The dosing interval should not be less than six hours.

Adults and adolescents (12 years and older)

An initial dose of two effervescent tablets of Metadol fizz equivalent to 75 mg tramadol hydrochloride and 650 mg paracetamol) is recommended. Additional doses can be taken as needed, not exceeding 8 effervescent tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day.

The dosing interval should not be less than six hours.

Metadol fizz should under no circumstances be administered for longer than is strictly necessary (see also section 4.4). If repeated use or long term treatment with Metadol fizz is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

Paediatric population

The effective and safe use of Metadol fizz has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Older people

A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency/dialysis

In patients with renal insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Hepatic impairment

In patients with hepatic impairment the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements (see section 4.4). Because of the presence of paracetamol Tramacet effervescent should not be used in patients with severe hepatic impairment (see section 4.3).

*Method of administration*

Oral use

Effervescent tablets should be taken dissolved in a glass of drinking water.

**4.3 Contraindications**

- Hypersensitivity to the active substances, sunset yellow or to any of the excipients listed in section 6.1,

- acute intoxication with alcohol, hypnotic medicinal products, centrally-acting analgesics, opioids or psychotropic medicinal products,

- Metadol fizz should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see section 4.5),

- severe hepatic impairment,

- epilepsy not controlled by treatment (see section 4.4).

**4.4 Special warnings and precautions for use**

*Warnings:*

- In adults and adolescents 12 years and older. The maximum dose of 8 tablets of Metadol fizz 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 products concurrently without the advice of a physician.

- In severe renal insufficiency (creatinine clearance <10 ml/mm), Metadol fizz is not recommended.

- In patients with severe hepatic impairment Metadol fizz 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, Metadol fizz is not recommended.

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

- Convulsions have been reported in tramadol hydrochloride-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with Metadol fizz only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol hydrochloride at the recommended dose levels. The risk may be increased when doses of tramadol hydrochloride exceed the recommended upper dose limit.

- 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 apnea (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.

*Precautions for use*

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

Concomitant use of Metadol fizz and sedative medicines such as benzodiazepines or related drugs 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 Metadol fizz 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).

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). In opioid-dependent patients and patients with a history of drug abuse or dependence, treatment should only be for short period and under medical supervision. Metadol fizz should be used with caution in patients with cranial trauma, in patients prone to convulsive disorder, biliary tract disorders, in a state of shock, in an altered state of consciousness for unknown reasons, with problems affecting the respiratory center or the respiratory function, or with an increased intracranial pressure.

Paracetamol in overdose may cause hepatic toxicity in some patients.

Symptoms of withdrawal reaction, similar to those occurring during opiate withdrawal, may occur even at therapeutic doses and for short term treatment (see section 4.8). Withdrawal symptoms may be avoided by tapering it at the time of discontinuation especially after long treatment periods. Rarely, cases of dependence and abuse have been reported (see section 4.8).

In one study, use of tramadol hydrochloride during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol hydrochloride during light planes of anaesthesia should be avoided.

The colorant Sunset yellow E110 may cause allergic reactions.

This medicinal product contains 179.4 mg of sodium per effervescent tablet, equivalent to 9.1% of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product (8 effervescent tablets) is equivalent to 73% of the WHO recommended maximum daily intake for sodium.

Tramacet is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

**4.5 Interaction with other medicinal products and other forms of interaction**
*Concomitant use is contraindicated with:*

• Non-selective MAO Inhibitors

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

• Selective-A MAO Inhibitors

Extrapolation from non-selective MAO inhibitors

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

• Selective-B MAO Inhibitors

Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusional state, even coma.

In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol hydrochloride

*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.

Avoid intake of alcoholic drinks and of medicinal products containing alcohol.

• Carbamazepine and other enzyme inducers

Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.

• Opioid agonists-antagonists (buprenorphine, nalbuphine, pentazocine)

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 re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

• Concomitant therapeutic use of tramadol hydrochloride and serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), 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 drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

• Other opioid derivatives (including antitussive medicinal products and substitutive treatments). Increased risk of respiratory depression which can be fatal in cases of overdose.

• Other central nervous system depressants, such as other opioid derivatives (including antitussive medicinal products and substitutive treatments), other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive medicinal products, thalidomide and baclofen.

These active substances can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.

• Sedating medicinal products such as benzodiazepines or related substances:

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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)

• As medically appropriate, periodic evaluation of prothrombin time should be performed when Tramacet and warfarin like compounds are administered concurrently due to reports of increased INR.

• In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT3 antagonist ondansetron increased the requirement of tramadol hydrochloride in patients with postoperative pain.

**4.6 Fertility, pregnancy and lactation**

*Pregnancy*

Since Metadol fizz is a fixed combination of active substances including tramadol hydrochloride, it should not be used during pregnancy.

• Data regarding paracetamol:

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

• Data regarding tramadol hydrochloride:

Tramadol hydrochloride should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol hydrochloride in pregnant women. Tramadol hydrochloride administered before or during birth does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

*Breast-feeding:*

Since Metadol fizz is a fixed combination of active ingredients including tramadol hydrochloride, it should not be ingested during breast feeding.

• Data regarding paracetamol:

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only paracetamol.

• Data regarding tramadol hydrochloride:

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. 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 breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

*Fertility*

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

Animal studies did not show an effect of tramadol on fertility. No study on fertility was accomplished with the combination of tramadol and paracetamol

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

Tramadol may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely

**4.8 Undesirable effects**

The most commonly reported undesirable effects during the clinical trials performed with the paracetamol/tramadol hydrochloride combination were nausea, dizziness and somnolence, observed in more than 10 % of the patients.

The frequencies are defined as follows:

| | |
|---|---|
| Very common: | ≥1/10 |
| Common: | ≥1/100 to <1/10 |
| Uncommon: | ≥1/1000 to <1/100 |
| Rare: | ≥1/10 000 to <1/1000 |
| Very rare: | <1/10 000 |
| Unknown: | Frequency cannot be estimated from the available data |

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

*Cardiac disorders:*

• Uncommon: arrhythmia, tachycardia, palpitations.

*Eye disorders:*

• Rare: vision blurred, miosis, mydriasis

*Ear and labyrinth disorders:*

• Uncommon: tinnitus

*Gastrointestinal disorders:*

• Very common: nausea

• Common: vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence

• Uncommon: dysphagia, melaena.

*General disorders and administration site conditions:*

• Uncommon: chills, chest pain.

*Investigations:*

• Uncommon: transaminases increased.

*Metabolism and nutrition disorders:*

• Unknown: hypoglycaemia

*Nervous system disorders:*

• Very common: somnolence, dizziness

• Common: headache, trembling

• Uncommon: muscular contractions involuntary, paraesthesia, amnesia

• Rare: convulsions, ataxia, syncope, speech disorders.

*Psychiatric disorders:*

• Common: confusional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders

• Uncommon: depression, hallucinations, nightmares

• Rare: delirium, drug dependence

Post marketing surveillance

Very rare: abuse.

*Renal and urinary disorders:*

• Uncommon: albuminuria, micturition disorder (dysuria and urinary retention).

*Respiratory, thoracic and mediastinal disorders:*

• Uncommon: dyspnoea

*Skin and subcutaneous tissue disorders:*

• Common: hyperhidrosis, pruritus

• Uncommon: dermal reactions (e.g.rash, urticaria).

*Vascular disorders:*

• Uncommon: hypertension, hot flush

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

**Tramadol hydrochloride**

• Postural hypotension, bradycardia, collapse.

• Post-marketing surveillance of tramadol hydrochloride has revealed rare alterations of warfarin effect, including elevation of prothrombin times.

• Rare cases (≥ 1/10000 to < 1/1000): allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis

• Rare cases (≥ 1/10000 to < 1/1000): changes in appetite, motor weakness, and respiratory depression

• Psychic side-effects may occur following administration of tramadol hydrochloride which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood, (usually euphoric mood occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders).

• Worsening of asthma has been reported though a causal relationship has not been established.

• Symptoms of drug withdrawal syndrome, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

**Paracetamol**

• Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

• There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

• Very rare cases of serious skin reactions have been reported.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

**4.9 Overdose**

Tramacet is a fixed combination of active substances. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol hydrochloride or paracetamol or of both these active ingredients.

*Symptoms of overdose from tramadol hydrochloride:*

In principle, on intoxication with tramadol hydrochloride, 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.

*Symptoms of overdose from paracetamol:*

An overdose is of particular concern in young children. Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalophathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis 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.

Emergency treatment:

- Transfer immediately to a specialised unit.

- Maintain respiratory and circulatory functions

- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.

- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.

- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.

- 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 hydrochloride is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with Tramacet with haemodialysis or haemofiltration alone is not suitable for detoxification.

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any adult or adolescent who had ingested around 7.5 g or more of paracetamol in the preceding 4 hours or any child who has ingested ≥150 mg/kg of paracetamol in the preceding 4 hours should undergo gastric lavage. Paracetamol concentrations in blood should be measured later than 4 hours after overdose in order to be able to assess the risk of developing liver damage (via the paracetamol overdose nomogram). Administration of oral methionine or intravenous N-acetylcysteine (NAC) which may have a beneficial effect up to at least 48 hours after the overdose, may be required. Administration of intravenous NAC is most beneficial when initiated within 8 hours of overdose ingestion. However, NAC should still be given if the time to presentation is greater than 8 hours after overdose and continued for a full course of therapy. NAC treatment should be started immediately when massive overdose is suspected. General supportive measures must be available.

Irrespective of the reported quantity of paracetamol ingested, the antidote for paracetamol, NAC, should be administered orally or intravenously, as quickly as possible, if possible, within 8 hours following the overdose.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids in combination with non-opioid analgesics; tramadol and paracetamol

ATC code: N02A J 13

**ANALGESICS**

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonists 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. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

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

Tramacet is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

### 5.2 Pharmacokinetic properties

Tramadol hydrochloride is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

After a single oral administration of a tramadol hydrochloride/paracetamol (37.5 mg/325 mg) effervescent tablet, mean peak plasma concentrations of 94.1 ng/ml for racemic tramadol and 4.0 mcg/ml for paracetamol are reached after 1.1 h (racemic tramadol) and 0.5 h (paracetamol), respectively. The mean terminal phase half-lives (t1/2) are 5.7 h for racemic tramadol and 2.8 h for paracetamol.

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Metadol fizz, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

*Absorption:*

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

After administration of Metadol fizz, 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 hydrochloride.

The oral administration of Metadol fizz with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that Metadol fizz can be taken independently of meal times.

*Distribution:*

Tramadol has a high tissue affinity (Vd,β=203 ± 40 l). It has a plasma protein binding of about 20%.

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.

*Metabolism:*

Tramadol is extensively metabolized after oral administration. About 30% of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

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 drug. 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 is principally metabolized 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 metabolized by cytochrome P 450 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. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is 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 preclinical study has been performed with the fixed combination (tramadol hydrochloride and paracetamol) to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the medicine has been observed in the progeny of rats treated orally with the combination tramadol hydrochloride/paracetamol.

The combination tramadol hydrochloride/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol hydrochloride/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect (10/87 and 25/217 mg/kg tramadol hydrochloride/paracetamol) did not result in toxic effects in the embryo or the foetus.

Results of standard mutagenicity tests did not reveal a potential genotoxic risk for tramadol hydrochloride in man.

Results of carcinogenicity tests do not suggest a potential risk of tramadol hydrochloride for man.

Animal studies with tramadol hydrochloride revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with maternotoxicity. Fertility reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. Male and female fertility was not affected.

Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic (i.e. non-toxic) doses.

Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Citric Acid Anhydrous
Sodium Bicarbonate
PVP K-30
Sodium Saccharin
Simethicone
Tween-80
Sodium Carbonate
Sodium Benzoate
Aspartame
PEG 8000
Orange Flavor
IPA
Purified water

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 Months

### 6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.
Keep out of reach and sight of children.

**6.5 Nature and contents of container**
4 Tablets packed in one ALU-ALU blister such 4 blister packed in a carton with insert.

**6.6 Special precautions for disposal and other handling**
Not applicable.

**7. Marketing Authorization Holder:--**
VOVANTIS LABORATORIES PVT. LTD.
Opp. Ranoli Railway Station,
Nr. GACL Plant, Ranoli,
Vadodara – 391 350
Gujarat, INDIA

**8. Manufactured By:--**
VOVANTIS LABORATORIES PVT. LTD.
Opp. Ranoli Railway Station,
Nr. GACL Plant, Ranoli,
Vadodara – 391 350
Gujarat, INDIA
**Date of revision of text: 20$^{h}$ April, 2021**