SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

ANTALGEX T 37.5 mg/325 mg, capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains: 37.5 mg tramadol hydrochloride and 325 mg paracetamol.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ANTALGEX T is indicated for the symptomatic treatment of moderate to severe pain.
The use of ANTALGEX T should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see section 5.1).

4.2 Posology and method of administration

Posology
The use of ANTALGEX T should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol.
The dose should be individually adjusted according to the intensity of the pain and to the sensibility of the patient. In general, the lowest dose producing analgesic effect should be selected.
A total daily dose of 8 capsules (equivalent to 300 mg of tramadol and 2600 mg of paracetamol) should not be exceeded. The dosing interval should not be less than 6 hours.

Adults and adolescents (over 12 years old)
An initial dose of two capsules of ANTALGEX T is recommended. Additional doses can be taken as needed, not exceeding 8 capsules (equivalent to 300 mg of tramadol and 2600 mg of paracetamol) per day.
The dosing interval should not be less than 6 hours.

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

Paediatric population
The effective and safe use of ANTALGEX T has not been established in children below the age of 12 years old. The treatment is therefore not recommended in this population.

Geriatric population
A dosing adjustment is generally not required in patients aged 75 years old or less without clinically manifest hepatic or renal insufficiency. In patients over 75 years old, the elimination may be extended. Then, if required, the dosing interval should be prolonged in terms of the patient's needs.

Renal failure/dialysis
The elimination of tramadol is delayed in patients with renal insufficiency. In those patients, a prolongation of the dosing intervals should be considered carefully in terms of the patient's needs.

Hepatic failure
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 patient's requirements (see section 4.4). Because of the presence of paracetamol, ANTALGEX T should not be used in patients with severe hepatic impairment (see section 4.3).

Method of administration
Oral use.
Capsules should be swallowed whole, with a sufficient amount of beverage.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients mentioned in section 6.1.
- Acute intoxication with alcohol, hypnotic medicines, centrally-acting analgesics, opioids or psychotropic medicines,
- ANTALGEX T should not be administered to patients who simultaneously are receiving or were being treated within two weeks with MonoAmine Oxidase Inhibitors (MAOIs) (see section 4.5 Interaction with other medicinal products and other forms of interactions),
- Severe hepatic impairment,
- Epilepsy not controlled by any treatment (see section 4.4 Special warning and precautions for use).

4.4. Special warnings and precautions for use

Warnings
- In adults and adolescents over 12 years, the maximum dose of 8 capsules of ANTALGEX T should not be exceeded. In order to avoid accidental overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter medicines) or tramadol hydrochloride containing products concurrently without the advice of a physician.
- In severe renal insufficiency (creatinine clearance <10 ml/min), ANTALGEX T is not recommended.
- In patients with severe hepatic impairment ANTALGEX T 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, ANTALGEX T is not recommended.

- Tramadol is not suitable as a substitute in opioid-dependent treatment patients. Although it is an opioid receptor agonist, tramadol cannot suppress morphine withdrawal symptoms.
- Convulsions have been reported in tramadol -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 anaesthesics. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with ANTALGEX T only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended maximum dose limit.
- Concomitant administration of opioids agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5 Interactions with other medicinal products and other forms of interactions).

Sleep-related breathing disorders
Opioids can cause sleeping-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioids use increase the risk of CSA in a dose-dependent manner. In patients who present CSA, consider decreasing the total opioids dosage.

Serotonin syndrome
Serotonin syndrome, potentially life-threatening syndrome, has been reported in patients treated with tramadol in association with other serotonin agents or by tramadol alone (see sections 4.5, 4.8 and 4.9)
If a concomitant treatment with others serotonin medicines is justified on the clinical plan, it is advice to monitor closely the patient, especially a the installation of the treatment and dose incrementation.

Symptoms of serotonin syndrome can include modification of the mental state, autonomous instability, neuromuscular anomalies and/or gastrointestinal symptoms.

In case of suspicion of serotonin syndrome, dose reduction or discontinuation of the treatment should be considered depending on the severity of the symptoms. Withdrawal of the serotonin medicines generally bring a rapid improvement.

CYP2D6 metabolism
Tramadol is metabolised by the liver enzyme CYP2D6. If a patient has a deficiency or is completely lacking this enzyme the adequate analgesic effect may not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is a risk of developing side effects of opioids toxicity event even at commonly prescribed doses.
General symptoms of opioids toxicity include confusion, drowsiness, shallow breathing, constricted pupils, nausea, vomiting, constipation and lack of appetite. In severe cases, this may include symptoms of circulatory and respiratory depression, which may be life threatening and fatal in very rarely cases.
Prevalence estimates of ultra-rapid metabolisers in different populations are summarised below:

Population	Prevalence %
African/ Ethiopian	29%
African American	From 3,4% to 6,5%
Asian	From 1,2% to 2%
Caucasian	From 3,6% to 6,5%

Greek	6 ,0%
Hungarian	1,9%
Northern European	From 1 % to 2%

Post-operative use in children
Literature report cases of tramadol given post-operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnea, led to rare but life threatening adverse events. Extreme caution should be exercised when tramadol is administered to children for post-operative pain relief and should be accompanied by close monitoring for symptoms of opioid toxicity including respiratory depression.

Children with compromised respiratory function
Tramadol is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of opioid toxicity.

Adrenal gland insufficiency
Opioid analgesics can occasionally cause reversible adrenal gland insufficiency needing a monitoring and a glucocorticoid substitute treatment. Symptoms of acute or long term adrenal gland insufficiency can include, for example, severe abdominal pain, nausea, vomiting, hypotension, extreme fatigue, decrease of appetite and weight loss.

Precautions for use
Risk from concomitant use of sedative medicines such as benzodiazepines and related drugs:
Concomitant use of ANTALGEX T 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 drugs should be reserved for patients for whom no other alternative treatment options exists. If a decision is made to prescribe ANTALGEX T 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).

Besides tolerance, psychic and physical dependence may develop, even at therapeutic doses and especially after long-term use. The clinical need for an analgesic treatment should be regularly reassessed (see section 4.2). In patients with opioid dependence and with history of drug abuse or dependence, the treatment should be administered only for a short duration and under medical supervision. ANTALGEX T should be used with caution in patients with cranial trauma, in patients with predispositions to seizure disorders, in patients with biliary tract dysfunctions, in state of shock, consciousness alteration from unknown origin, respiratory centre or respiratory function disorders or with an increased intracranial pressure.

Paracetamol overdosage may cause hepatic toxicity in some patients.

Withdrawal symptoms similar to those occurring during opiates withdrawal might occur even at therapeutically doses or for short duration (see section 4.8). When a patient no longer requires treatment with ANTALGEX T, it may be advisable to reduce the dose gradually to prevent

symptoms of withdrawal, especially after long treatment periods. Rare cases of dependence and abuse have been reported (see section 4.8).

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

4.5. Interactions with other medicinal products and other forms of interaction

Concomitant use is contraindicated with
• Non-selective MAO Inhibitors
Risk of serotoninergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusion, even coma.
• Selective-A MAO Inhibitors
Extrapolation from non-selective MAO inhibitors
Risk of serotoninergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusion, even coma.
• Selective-B MAO Inhibitors
Central excitation symptoms evocative of a serotoninergic syndrome: diarrhoea, tachycardia, hyperhidrosis, trembling, confusion, even coma**.**

In case of recent treatment with MAO inhibitors, a delay of two weeks should be respected before starting treatment with tramadol.

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 medicinal products containing alcohol.
• Carbamazepine and other enzyme inducers
Risk of decreased efficiency and action duration because of the decreased plasma concentration 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 cause convulsions and increase the convulsing potential of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other medicines that lower the seizure threshold (as bupropion, mirtazapine, tetrahydrocannabinol).
- The concomitant therapeutic use of tramadol and serotoninergic medicines as serotonin reuptake inhibitors (SSRIs), serotonin- norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine, might cause a serotoninergic syndrome, potentially life-threatening syndrome (see sections 4.4 and 4.8).
- Other opioids derivatives (including antitussives and substitutive treatments)
  Increased risk of respiratory depression which can be fatal in cases of overdose.
- Other central nervous system depressants such as other opioids analgesics (including antitussives and substitutive treatments), other anxiolytics, hypnotics, sedative

antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.
These medicines can cause increased central depression. The effect on alertness can make driving vehicles or the use of machines dangerous.

- Sedating medicines products such as benzodiazepines and 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 due to the cumulative CNS depressant effects. The dose and duration of the concomitant use should be limited (see section 4.4).
- Depending on clinical needs, an assessment of prothrombin time should be carried out in case of co-administration of ANTALGEX T with warfarin derivatives, INR extensions having been reported.
- In a limited number of studies, the pre- or postoperative application of the antiemetic 5-HT3 antagonist (ondansetron) increased the need of tramadol in patients with postoperative pain.

4.6. Fertility, pregnancy and lactation

Pregnancy
Since ANTALGEX T is a fixed combination of active substances including tramadol, it should not be administered during pregnancy.

- *Data regarding paracetamol:*
  Studies in animals are insufficient to conclude on reproductive toxicity. A large amount of data on pregnant women indicate neither malformative, nor foeto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol *in utero* show inconclusive results.
- *Data regarding tramadol:*
  There is not enough pertinent data available to evaluate the safe use in pregnant women.
  Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which however 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:
ANTALGEX T being a fixed combination of active ingredients containing tramadol, this medicine should not be used during breast-feeding or alternatively, breast-feeding should be discontinued during treatment with ANTALGEX T. Discontinuation of breast-feeding is generally not necessary following a single dose of ANTALGEX T.

- *Data on paracetamol:*
  Paracetamol is excreted in breast milk but not in a clinically significant amount.
- *Data on tramadol:*
  About 0.1 % of the dose of tramadol administered to the mother is excreted in breast milk. During the immediate post-partum period, for a daily oral dose up to 400 mg administered to the mother, corresponds in the nursed infant to 3 % of the maternal weight-adjusted dose. Therefore, tramadol should not be used during breast-feeding, or breast-feeding should be interrupted in case of tramadol treatment. Discontinuation of breast-feeding is generally not required in case of a single administration of tramadol.

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

Animal studies did not demonstrate an effect of tramadol on fertility. No study on fertility was conducted with a 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 nor operate machinery.

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 drowsiness, observed in more than 10 % of the patients.

The frequencies are defined as follows:

Very common	≥1/10
Common	≥1/100, < 1/10
Uncommon	≥ 1/1,000, < 1/100
Rare	≥/10,000, <1/1,000
Very rare	<1/10,000
Undetermined frequency	which cannot be estimated based on the available data.

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

Cardiovascular disorders:
• Uncommon: palpitations, tachycardia, arrhythmia.
Eye disorders:
• Rare: blurred vision, miosis, mydriasis.
Ear and labyrinth disorders:
• Uncommon: tinnitus.
Gastrointestinal disorders:
• Very common: nausea.
• Common: vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, gas.
• Uncommon: dysphagia, melaena.
General disorders and administration site conditions:
• Rare: chills, chest pain.
Investigations:
• Uncommon: transaminases increased
Metabolism and nutrition disorders:
• Undetermined frequency: hypoglycaemia.
Nervous system disorders:
• Very common: dizziness, drowsiness.
• Common: headache, trembling.
• Uncommon: involuntary muscular contractions, paraesthesia, amnesia.
• Rare: ataxia, convulsions, syncope, speech disorders.
Psychiatric disorders:
• Common: confusion state, mood altered (anxiety, nervousness, euphoria), sleep disorders.
• Uncommon: depression, hallucinations, nightmares.
• Rare: delirium, drug dependence.

Post-marketing surveillance:
• Very rare: abuse.
Renal and urinary disorders:
• Uncommon: albuminuria, micturition disorders (dysuria and urinary retention).
Respiratory, thoracic and mediastinal disorders:
• Uncommon: dyspnoea.
Skin and subcutaneous tissue disorders:
• Common: hyperhidrosis, pruritus.
• Uncommon: skin reactions (i.e. rash, hives).
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 or paracetamol cannot be excluded:

Tramadol
• Postural hypotension, bradycardia, collapse (tramadol).
• Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
• Rare cases (≥ 1/10.000 to < 1/1.000): allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis.
• Rare cases (≥ 1/10.000 to < 1/1.000): changes in appetite, motor weakness, and respiratory depression.
• Psychic side-effects may occur following administration of tramadol 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 capacities (e.g. decision behaviour, perception disorders).
•Nervous system affection: unknown frequency: Serotonin syndrome.
• Worsening of asthma has been reported though a causal relationship has not been established.
• Symptoms of drug withdrawal syndrome, similar to those occurring during opioids 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 attacks, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.
• Respiratory, thoracic and mediastinal disorders: undetermined: hiccup.

Paracetamol
• Despite the fact that the undesirable effects are rare, hypersensitivity including skin rash may occur. Cases of blood dyscrasias have been reported, including thrombocytopenia and agranulocytosis, but the causality relation with paracetamol has not been established in all cases.
• Several reports suggest that paracetamol could induce a hypoprothrombinaemia in case of concomitant administration with warfarin-like compounds. In other studies, the prothrombin time has not been modified.
• Severe skin reactions have been reported in very rare cases.

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 national reporting system.

4.9. Overdose

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

Symptoms of overdose from tramadol:

In principle, when intoxicated with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include mostly, miosis, vomiting, cardiovascular collapse, consciousness disorders that can lead to coma, convulsions and respiratory depression up to respiratory arrest.
Serotonin syndrome also has been reported.

Symptoms of overdose from paracetamol:

An overdose is of particular concern in young children.
Symptoms of paracetamol overdose in the first 24 hours are the following: 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 encephalopathy, 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) could become irreversibly bounded 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 the hepatic function tests.
• Perform hepatic function tests as soon as possible and repeat every 24 hours. Usually, 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) 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 is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with ANTALGEX T 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. 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 plasmatic concentrations 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 life supportive measures must be put in place.

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: Other opioids; Tramadol in combination,
ATC code: **N02AJ13**

ANALGESICS
Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is 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 influenced. 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 remains unknown and may involve central and peripheral effects.
ANTALGEX T is positioned as a step II analgesic in the WHO pain ladder and should be used 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), mean peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 μg/ml for paracetamol are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol), respectively. The mean elimination half-lives (t1/2) are 5.1/4.7 h for racemic tramadol and 2.5 h for paracetamol.

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of tramadol/paracetamol, 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 ANTALGEX T, 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 ANTALGEX T with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that ANTALGEX T can be taken independently of meal times.

Distribution
Tramadol has a high tissue affinity ($V_{d,\beta}$=203 ± 40 liters). 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 (about 20%) of paracetamol is bound to plasma proteins.

Biotransformation
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 are unlikely to change on multiple dosing.
Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The second 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 benzoquinone imine) 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 toxic 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

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.
No preclinical study has been performed with the fixed combination (tramadol 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 offspring of rats treated orally with the combination tramadol/paracetamol.
The combination tramadol/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 human. 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/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 for human.
Animal studies with tramadol 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.
To this day, animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Capsule: Dibasic calcium phosphate, magnesium stearate.
Capsule shell: gelatine, titanium dioxide (E171).

6.2. Incompatibilities
Not applicable.

6.3. Shelf-life
3 years.

6.4.Special precautions for storage
Store in the original package, protect from heat, light and moisture
Store below 30°C

6.5. Nature and contents of container
ANTALGEX T is available in boxes of 20 capsules.
ANTALGEX T capsules are packed in PVC/Aluminium blisters.

6.6. Special precautions for disposal and other handlings
No special requirements.

7. CATEGORY OF DISTRIBUTION

☐ Over-the counter medicine ☒ Prescription only medicines
List I

8. MARKETING AUTHORISATION HOLDER

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Zoning Industriel de Nivelles Sud, zone II
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9. MANUFACTURER

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10. UPDATE DATE

February 2022.