Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tramadol / Paracetamol 75 mg / 650 mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release tablet contains 75 mg tramadol hydrochloride and 650 mg paracetamol.

Excipients: Each tablet contains 0.09 mg sunset yellow (E110).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

Bi-layered biconvex oval shaped film-coated tablets, consisting of an immediate-release layer (light peach) and a prolonged-release layer (white to off-white).

The tablets are embossed “DDS 082” on the face of light peach layer.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

DDS-06C tablets are indicated for the symptomatic treatment of moderate to severe pain in adults and adolescents over the age of 12 years.

The use of DDS-06C 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

Adults and adolescents (12 years and older)

The use of DDS-06C 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 intensity of pain and response of the patient.

An initial dose of one or two tablets of DDS-06C (equivalent to 75 mg or 150 mg of tramadol hydrochloride and 650 mg or 1300 mg of paracetamol) is recommended. Additional doses can be taken as needed, not exceeding four tablets (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should not be less than twelve hours.

DDS-06C should under no circumstances be administered for longer than is strictly necessary (see section 4.4). If repeated use or long term treatment with DDS-06C 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.

Children (under 12 years)

The effective and safe use of DDS-06C has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

Elderly patients

The usual dosages may be used in elderly 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. Dosing should be monitored in this population.

Renal insufficiency

Because of the presence of tramadol, the use of DDS-06C is not recommended in patients with severe (creatinine clearance < 10 ml/min) or moderate renal insufficiency (creatinine clearance between 10 and 30 ml/min), however, in cases of moderate renal insufficiency where the potential benefit outweighs the risk, an increase in the dosing interval should be carefully considered. Close monitoring of these patients is recommended.

As tramadol is removed only very slowly by haemodialysis or by haemofiltration, post dialysis administration to maintain analgesia is not usually required.

Hepatic insufficiency

Use of DDS-06C in patients with hepatic impairment has not been studied. In patients with severe hepatic impairment DDS-06C use is contraindicated (see section 4.3). Use of DDS-06C is not recommended in patients with moderate hepatic impairment, in cases of moderate hepatic impairment where the potential benefit outweighs the risk, an increase in the dosing interval should be carefully considered. Regular monitoring of these patients should take place to assess whether continuation of the treatment is appropriate (see section 4.4).

Method of administration

Oral use

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

4.3 Contraindications

- Hypersensitivity to tramadol, paracetamol or to any of the excipients (see section 6.1) of the medicinal product,
- Acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs,
- DDS-06C 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, the maximum dose of 4 tablets of DDS-06C 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 moderate to severe renal insufficiency (creatinine clearance <10 ml/mm), DDS-06C is not recommended.
- In patients with severe hepatic impairment use of DDS-06C is contraindicated (see section 4.3). Use of DDS-06C is not recommended in patients with moderate hepatic impairment cases. In cases of moderate hepatic impairment where the potential benefit outweighs the risk, an increase in the dosing interval should be carefully considered. Regular monitoring of these patients should take place to assess whether continuation of the treatment is appropriate.

The hazards of paracetamol overdose are greater in patients with non-cirrhotic alcoholic liver disease.

- In severe respiratory insufficiency, DDS-06C is not recommended.
- Tramadol is not suitable as a substitute in opioid-dependent patients. Although it is an opioid agonist, tramadol cannot suppress morphine withdrawal symptoms.
- Convulsions 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 anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with DDS-06C 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 upper dose limit.
- Concomitant use of opioid agonists-antagonists (nalbuphine, buprenorphine, pentazocine) is not recommended (see section 4.5).

Precautions for use:

DDS-06C should be used with caution in opioid dependent patients, or 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 overdosage may cause hepatic toxicity in some patients.

At therapeutic doses, tramadol has the potential to cause withdrawal symptoms. Rarely, cases of dependence and abuse have been reported (see section 4.8).

Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur (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 planes of anaesthesia should be avoided.

DDS-06C contains the colouring agent, sunset yellow E110, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use is contraindicated with:

- Non-selective MAO Inhibitors:
  Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.
- Selective-A MAO Inhibitors:
  Extrapolation from non-selective MAO inhibitors
  Risk of serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.
- Selective-B MAO Inhibitors:
  Central excitation symptoms evocative of a serotoninergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.
  In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before 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 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:

- In isolated cases there have been reports of Serotonin Syndrome in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicines such as selective serotonin re-uptake inhibitors (SSRIs) and triptans. Signs of Serotonin Syndrome may be for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.
- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates.
- 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 drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen.
- These drugs can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
- As medically appropriate, periodic evaluation of prothrombin time should be performed when DDS-06C and warfarin like compounds are administered concurrently due to reports of increased INR.
- Other drugs known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.
- Medicinal products reducing the seizure threshold, such as bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics. Concomitant use of tramadol with these drugs can increase the risk of convulsions. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
- In a limited number of studies the pre- or postoperative application of the antiemetic 5−HT3 antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Since DDS-06C is a fixed combination of active ingredients including tramadol, 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:
- Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol 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 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.

Lactation:

Since DDS-06C is a fixed combination of active ingredients including tramadol, 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:
  Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol should not be ingested during breast-feeding.

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.

4.8 Undesirable effects

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

The frequency of undesirable effects is defined using the following conventions:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000, <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).

Psychiatric disorders
- Common: confusion, mood changes (anxiety, nervousness, euphoria), sleep disorders
- Uncommon: depression, hallucinations, nightmares, amnesia
- Rare: drug dependence

Post marketing surveillance
- Very rare: abuse

Nervous system disorders
- Very common: dizziness, somnolence
- Common: headache, trembling
- Uncommon: involuntary muscular contractions, paraesthesia, tinnitus
- Rare: ataxia, convulsions

Eye disorders
- Rare: blurred vision

Cardiac disorders
- Uncommon: palpitations, tachycardia, arrythmia

Vascular disorders
- Uncommon: hypertension

Respiratory, thoracic and mediastinal disorders:
- Uncommon: dyspnoea

Gastrointestinal disorders
- Very common: nausea
- Common: vomiting, constipation, dry mouth, diarrhoea abdominal pain, dyspepsia, flatulence
- Uncommon: dysphagia, melaena

Hepatobiliary disorders
- Uncommon: hepatic transaminases increase

Skin and subcutaneous tissue disorders
- Common: sweating, pruritus
- Uncommon: dermal reactions (e.g., rash, urticaria)

Renal and urinary disorders
- Uncommon: albuminuria, micturition disorders (dysuria and urinary retention)

General disorders and administration site conditions
- Uncommon: shivers, hot flushes, thoracic pain

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: allergic reactions with respiratory symptoms (e.g., dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
- Rare cases: 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 elation 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 withdrawal reactions, 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.

4.9 Overdose

DDS-06C is a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

Symptoms of overdose from tramadol:

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

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 is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with DDS-06C 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 ³150 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: Tramadol, combinations, ATC code: N02A X 52.

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.

DDS-06C is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

5.2 Pharmacokinetic properties

Absorption:
Tramadol is 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%. Following a single oral administration of DDS-06C under fasting conditions, the peak plasma tramadol concentration (296 ± 61 ng/mL) was reached after 5 hours and the mean elimination half-life ($t_{1/2z}$) is 6.8 hours.

After administration of DDS-06C the oral absorption of paracetamol is nearly complete. Following a single oral administration of DDS-06C under fasting conditions, the peak plasma paracetamol concentration (8.9 ± 2.2 µg/mL) was reached within 1 hour and the mean elimination half-life ($t_{1/2z}$) is 6.1 hours.

The oral administration of DDS-06C with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol. DDS-06C can be taken independently of meal times.

Distribution:
Tramadol has a high tissue affinity ($V_{d,\beta}$=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 P450 to an active intermediate (the N−acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination:
Tramadol and its metabolites are eliminated mainly by the kidneys. Following a single dose of DDS-06C the half-life of paracetamol is approximately 6 hours in adults. The half-life of paracetamol 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 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/paracetamol.

The combination tramadol/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/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/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 in man.

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

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. No effect on fertility has been observed after oral administration of tramadol up to doses of 50 mg/kg in the male rat and 75 mg/kg in the female rat.

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

Tablet core:
Microcrystalline cellulose
Croscarmellose sodium
Silica colloidal anhydrous
Sodium stearyl fumarate

Sunset yellow E110
Hydroxypropyl distarch phosphate (E1442)
Copovidone
Pregelatinised maize starch
Hypromellose type 2208

Film-coating:
Polydextrose
Hypromellose
Talc
Maltodextrin
Medium chain triglycerides

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PCTFE (Aclar®) blisters with aluminium backing foil (containing 3, 5, 10, 15, 20, 30, 40, 50, 60, 90 or 100 prolonged-release tablets).

HDPE bottles with PP cap containing 60 or 180 prolonged-release tablets.

Not all packaging sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1246/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2013