SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tramadol Hydrochloride 50mg Effervescent Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Effervescent tablet contains 50mg Tramadol hydrochloride.

Excipients with known effect: Each effervescent tablet contains 75mg lactose (as lactose monohydrate) and 182mg sodium (see section 4.4)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Effervescent tablet

White round biplane effervescent tablet of approximate diameter of 17.8-18.3mm with a facet on both sides and a score line on one side.

4 CLINICAL PARTICULARS

4.1Therapeutic indications

The treatment and prevention of moderate to severe pain.

4.2 Posology and method of administration

As with all analgesic drugs, the dose of tramadol hydrochloride should be adjusted according to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.

<u>Adults and children aged 12 years and over:</u>
Acute pain - An initial dose of 100mg is usually necessary. This can be followed by doses of 50 or 100mg not more frequently than 4 hourly, and duration of therapy should be matched to clinical need.

Pain associated with chronic conditions - Use an initial dose of 50mg and then titrate dose according to pain severity. The need for continued treatment should be assessed at regular intervals as withdrawal symptoms and dependence have been reported (see section 4.4 - "Special Warnings and Precautions for Use").

A total oral daily dose of 400mg should not be exceeded except in special clinical circumstances.

Geriatric patients
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. It should be noted that in volunteers aged over 75 years the elimination halflife of tramadol was increased by approximately 17% following oral administration.

Renal insufficiency /renal dialysis/hepatic impairment:
In patients with renal and/or hepatic 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.
For patients with creatinine clearance of less than 30ml/min, the dosage interval should be increased to 12 hours. Tramadol is not recommended for patients with severe renal impairment where the creatinine clearance is less than 10ml/min.

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

In severe hepatic impairment the dosage interval should be increased to 12 hours.

Children under 12 years:
Tramadol hydrochloride capsules are not intended for administration to children under 12 years of age.

Duration of administration
Tramadol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with tramadol is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Method of administration For oral administration.

The capsules should be swallowed whole and not chewed. They should be taken with a little water before or after meals.

Treatment goals and discontinuation

Before initiating treatment with Tramadol, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with tramadol, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

4.3Contraindications

Tramadol hydrochloride is contraindicated:

- in hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- in cases of acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs
- in conjunction with monoamine oxidase inhibitor administration, or within two weeks of its withdrawal
- in patients with epilepsy not adequately controlled by treatment
- for use in narcotic withdrawal treatment
- in patients with porphyria
- during an asthmatic attack

4.4 Special warnings and precautions for use

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Tramadol. Repeated use of Tramadol can lead to opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of Tramadol may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with Tramadol and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behaviour (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

At therapeutic doses withdrawal symptoms have been reported at a reporting frequency of 1 in 8,000.

Tramadol should be used with caution in opioid-dependent patients, patients with head injury, a reduced level of consciousness of uncertain origin, disorders of the respiratory centre or function, increased intracranial pressure, severe impairment of hepatic and renal function and in patients prone to convulsive disorders or in shock.

In patients sensitive to opiates the product should only be used with caution.

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

Adrenal insufficiency
Opioid analgesics may occasionally cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of acute or chronic adrenal insufficiency may include e.g. severe abdominal pain, nausea and vomiting, low blood pressure, extreme fatigue, decreased appetite, and weight loss.

Tramadol should be prescribed with special care in patients with hypotension, prostatic hypertrophy and obstructive or inflammatory bowel disease.

Convulsions have been reported at therapeutic doses and the risk may be increased at doses exceeding the usual upper daily dose limit (400mg). Patients with a history of epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling reasons.
The risk of convulsions may increase in patients taking tramadol and concomitant medication that can lower the seizure threshold (see section 4.5 - Interactions with Other Medicinal Products and Other Forms of Interactions).

Care should be taken when treating patients with respiratory depression, or if concomitant CNS depressant drugs are being administered, (see section 4.5), or if the recommended dosage is significantly exceeded (see section 4.9) as the

possibility of respiratory depression cannot be excluded in these situations. At therapeutic doses respiratory depression has infrequently been reported.

In one study using a nitrous oxide/opioid (tramadol) anaesthetic technique (with only intermittent administration of enflurane "as required") tramadol was reported to enhance intra-operative recall. Hence its use during potentially very light planes of general anaesthesia should be avoided.

Two recent studies of tramadol administration during anaesthesia comprising continuous administration of isoflurane did not show clinically significant lightening of anaesthetic depth or intra-operative recall. Therefore providing the current practice of administering continuous, potent (volatile or intravenous) anaesthetic agent is followed, tramadol may be used intraoperatively in the same way as other analgesic agents are routinely used.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains 463mg sodium per dose (two tablets) equivalent to 23.1% of the WHO recommended maximum daily intake for sodium (2g).

The maximum daily dose of this product (eight tablets) is equivalent to 92.6% of the WHO recommended.

Tramadol Hydrochloride 50mg Effervescent Tablets are considered high in sodium This should be taken into account for those on a low salt diet.

Serotonin syndrome

Serotonin syndrome, a potentially life-threatening condition, has been reported in patients receiving tramadol in combination with other serotonergic agents or tramadol alone (see sections 4.5, 4.8 and 4.9).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose escalations.

Symptoms of serotonin syndrome may include mental status changes, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms. Withdrawal of the serotonergic drugs usually brings about a rapid improvement.

4.5 Interaction with other medicinal products and other forms of interaction

Tramadol should not be combined with MAO inhibitors. (see section 4.3).

In patients treated with MAO inhibitors in the 14 days prior to the use of the opioid pethidine, life-threatening interactions on the central nervous system, respiratory and cardiovascular function have been observed. The same interactions with MAO inhibitors cannot be ruled out during treatment with Tramadol.

Concomitant administration of tramadol with other centrally acting drugs, including alcohol, may potentiate CNS depressant effects. (see section 4.8).

The concomitant use of Tramadol with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death.

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs),serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), anti-psychotics and other seizure threshold lowering medicinal products(such as bupropion, mirtazapine, tetrahydrocannabinol*)* to cause convulsions (see section 4.4 - Special Warnings and Precautions for Use and section 5.2 – Pharmacokinetic properties). There is a theoretical possibility that tramadol could interact with lithium. There have been no reports of this potential interaction.
"Concomitant therapeutic use of tramadol 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 syndrome, a potentially life-threatening condition (see sections 4.4 and 4.8).

Pharmacokinetic studies were conducted to investigate the effects of cimetidine, (enzyme inhibitor) quinidine and carbamazepine (enzyme inducer) on the pharmacokinetics of tramadol.

Carbamazepine

Simultaneous or previous administration of carbamazepine (enzyme inducer) markedly decreases serum concentrations of tramadol to an extent that a decrease in analgesic effectiveness and a shorter duration of action may occur.

Cimetidine

With the concomitant or previous administration of cimetidine (enzyme inhibitor), clinically relevant interactions are unlikely to occur. Therefore no alteration of the tramadol dosage regimen is recommended for patients receiving chronic cimetidine therapy.

Quinidine

A study in 12 healthy volunteers has shown that quinidine causes an approximate 25 % increase in the tramadol C_{max} and AUC. T_{max} is unaffected. However, the increases in C_{max} and AUC fall within the normal therapeutic range for tramadol, and no dosage adjustment is required.

The combination with mixed agonist/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) and tramadol is not advisable, because the analgesic effect of a pure agonist may be theoretically reduced in such circumstances.

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 medicinal products such as selective serotonin re-uptake inhibitors (SSRIs) or with MAO inhibitors. Signs of serotonin syndrome may be for example confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

Caution should be exercised during concomitant treatment with tramadol and coumarin derivatives (e.g. warfarin) due to reports of increased INR with major bleeding and ecchymoses in some patients.

Other active substances 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 (see section 4.8).

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.

4.6Fertility, pregnancy and lactation

Pregnancy

Animal studies (rat and rabbit, exposure to tramadol up to 7 times that expected in humans) have revealed minimal embryo-toxicity (delayed ossification, effects on organ development and neonatal mortality). Teratogenic effects were not observed. Tramadol crosses the placenta. There is inadequate evidence available on the safety of tramadol in human pregnancy, therefore tramadol should not be used 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. Chronic use during pregnancy may lead to neonatal withdrawal symptoms.

Breast-feeding:

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 is not recommended during breast-feeding. After a single administration of tramadol it is not usually necessary to interrupt breast-feeding.

Fertility
Post marketing surveillance does not suggest an effect of tramadol on fertility. Animal studies did not show an effect of tramadol on fertility.

4.7 Effects on ability to drive and use machines

Even when taken according to instructions, Tramadol hydrochloride may cause drowsiness, somnolence and dizziness and therefore may impair the reactions of drivers and machine operators and this effect may be potentiated by other psychotropic substances, particularly alcohol and other CNS-depressants. Ambulant patients should be warned not to drive or operate machinery if affected.

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:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

4.8 Undesirable effects

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients.

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100) rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known: cannot be estimated from the available data

Cardiovascular disorders:
Uncommon: Cardiovascular regulation (palpitation, tachycardia, postural hypotension
cardiovascular collapse. These adverse reactions may occur especially on intravenous administration and in patients who are physically stressed Rare: increase in blood pressure, bradycardia

Eye disorders:
Rare: blurred vision, miosis, mydriasis

Gastro-intestinal disorders:
Very common: nausea

Common: vomiting, constipation, dry mouth
Uncommon: retching; gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea

Hepatobiliary disorders:
In a few isolated cases an increase in liver enzyme values has been reported in a temporal connection with the therapeutic use of tramadol.

Metabolism and nutrition disorders:
Rare: changes in appetite
Not known: hypoglycaemia

Musculoskeletal and connective tissue disorders:
Rare: motor weakness

Nervous system disorders:
Very common: dizziness
Common: headache, somnolence, drowsiness
Rare: paraesthesia, tremor, epileptiform, convulsion,
involuntary muscle contractions, abnormal coordination, syncope, speech disorders
Not known: Serotonin syndrome

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.
Epileptiform convulsions occurred mainly after administration of high doses of tramadol or after concomitant treatment with medicinal products which can lower the seizure threshold (see sections 4.4 and 4.5).

Respiratory, thoracic and mediastinal disorders:
Rare: dyspnoea , respiratory depression

If the recommended doses are considerably exceeded and other centrally depressant substances are administered concomitantly (see section 4.5), respiratory depression may occur.

Unknown: worsening of existing asthma, though a causal relationship has not been established, hiccups

General disorders and administration site conditions:
Common: fatigue

Psychiatric disorders:

Rare: confusion, hallucination, sleep disturbance, delirium, anxiety and nightmares,

Psychic adverse reactions may occur following administration of Tramadol which vary individually in intensity and nature (depending on personality and duration of treatment). 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).
Dependence may occur

Drug dependence:
Repeated use of Tramadol can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Physical dependence:
Dependence, abuse and withdrawal reactions have been reported. Typical opiate withdrawal reactions include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor & gastrointestinal symptoms (See section 4.4 – "Special Warnings and Special Precautions for Use" and 4.2 – "Posology and Method of Administration"). Other symptoms that have very rarely been seen with tramadol discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus and unusual CNS symptoms (i.e. confusion, delusions, depersonalisation, derealisation, paranoia).

Immune system disorders:
Rare: Anaphylaxis, allergic reactions (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema)

Skin and subcutaneous tissue disorders:
Common: Sweating (diaphoresis, hyperhidrosis)
Uncommon: dermal reactions (e.g. pruritus, skin rash, urticaria)

Renal and urinary disorders:
Rare: micturition disorder (difficulty in passing urine, dysuria and urinary retention)

Vascular disorders:
Rare: flushing, orthostatic hypotension,

Blood and lymphatic system disorders:
Cases of blood dyscrasias have been rarely observed during treatment with tramadol but causality has not been established.

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.

4.9Overdose

Symptoms of overdosage are typical of other opioid analgesics (centrally acting), and include miosis, vomiting, cardiovascular collapse, sedation and consciousness disorders up to coma, seizures and respiratory depression up to respiratory arrest.

Serotonin syndrome has also been reported.

Treatment -
The general emergency measures apply. 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. In animal experiments naloxone had no effect on convulsions, in such cases fits can be controlled with diazepam (intravenously).

In case of intoxication orally, gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after tramadol intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities or prolongedrelease formulations.

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

5 PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic properties

Tramadol is a centrally acting analgesic. It is a non-selective pure agonist at mu (μ), delta and kappa opioid receptors with a higher affinity for the mu (μ) receptor. Other mechanisms which may contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

Tramadol has an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight. The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine

5.2Pharmacokinetic properties

After oral administration, tramadol is almost completely (More than 90%) absorbed. Mean absolute bioavailability is approximately 70 % following a single dose and increases to approximately 90 % at steady state.
Tramadol has a high tissue affinity ($V_{d,ß}$= 203 ± 40 l). Plasma protein binding of tramadol is approximately 20 %. When C14-labelled tramadol was administered to humans, approximately 90 % was excreted via the kidneys with the remaining 10 % appearing in the faeces.

Tramadol has a linear pharmacokinetic profile within the therapeutic dose range. The relationship between serum concentrations and the analgesic effect is dose-dependent, but varies considerably in isolated cases. A serum concentration of 100 - 300 ng/ml is usually effective.

The half-life of the terminal elimination phase ($t^1/_2\beta$) was 6.0 ± 1.5h in young volunteers. Tramadol pharmacokinetics show little age dependence in volunteers up to the age of 75 years. In volunteers aged over 75 years, $t^1/_2\beta$ was 7.0 ± 1.6h on oral administration.

Following a single oral dose administration of tramadol 100 mg as capsules or tablets to young healthy volunteers, plasma concentrations were detectable within approximately 15 to 45 minutes with a mean C_{max} of 280 to 308 mcg/L and T_{max} of 1.6 to 2 h.

Tramadol passes the blood-brain and placental barriers. Very small amounts of the substance and its O-desmethyl derivative are found in the breast-milk (0.1 % and 0.02 % respectively of the applied dose).

Tramadol is metabolised by the cytochrome P450 isoenzyme CYP2D6. It undergoes biotransformation to a number of metabolites mainly by means of N- and O-demethylation. O-desmethyl tramadol appears to be the most pharmacologically active metabolite, showing analgesic activity in rodents. As humans excrete a higher percentage of unchanged tramadol than animals it is believed that the contribution made by this metabolite to analgesic activity is likely to be less in humans than animals. In humans the plasma concentration of this metabolite is about 25 % that of unchanged tramadol.

Since tramadol is eliminated both metabolically and renally, the terminal half-life $t^1/_2\beta$ may be prolonged in impaired hepatic or renal function. In patients with liver cirrhosis $t^1/_2\beta$ tramadol was a mean of 13.3 ± 4.9h; in patients with renal insufficiency (creatinine clearance ≤ 5 ml/min) it was 11.0 ± 3.2h.

5.3Preclinical safety data

On repeated oral and parenteral administration of tramadol for 6 - 26 weeks in rats and dogs and oral administration for 12 months in dogs, haematological, clinico-chemical and histological investigations showed no evidence of any substance-related changes. Central nervous manifestations only occurred after high doses considerably above the therapeutic range: restlessness, salivation, convulsions, and reduced weight

gain. Rats and dogs tolerated oral doses of 20 mg/kg and 10 mg/kg body weight respectively, and dogs' rectal doses of 20 mg/kg body weight without any reactions.
In rats tramadol dosages from 50 mg/kg/day upwards caused toxic effects in dams and raised neonate mortality. In the offspring retardation occurred in the form of ossification disorders and delayed vaginal and eye opening. Male fertility was not affected. After higher doses (from 50 mg/kg/day upwards) females exhibited a reduced pregnancy rate. In rabbits there were toxic effects in dams from 125 mg/kg upwards and skeletal anomalies in the offspring.
In some in-vitro test systems there was evidence of mutagenic effects. In-vivo studies showed no such effects. According to knowledge gained so far, tramadol can be classified as non-mutagenic.
Studies on the tumorigenic potential of tramadol hydrochloride have been carried out in rats and mice. The study in rats showed no evidence of any substance-related increase in the incidence of tumours. In the study in mice there was an increased incidence of liver cell adenomas in male animals (a dose-dependent, non-significant increase from 15 mg/kg upwards) and an increase in pulmonary tumours in females of all dosage groups (significant, but not dose-dependent).

In single and repeat –dose toxicity studies (rodents and dogs) exposure to tramadol 10 times that expected in man is required before toxicity (hepatotoxicity) is observed. Symptoms of toxicity are typical of opioids and include restlessness, ataxia, vomiting, tremor, dyspnoea and convulsions.

Exposure to tramadol (≥ that expected in man) in lifetime toxicity studies in rodents did not reveal any evidence of carcinogenic hazard, and a battery of in-vitro and in-vivo mutagenicity tests were negative.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous
Sodium hydrogen carbonate
Sodium sulfate, anhydrous
Lactose monohydrate
Macrogol 6000
Sodium carbonate, anhydrous
Polyvidone
Sodium cyclamate
Orange flavour CGI 00285
(containing E320 butylated hydroxyanisole)
Simethicone emulsion

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

White polypropylene tablet tube with a white polypropylene air-sec stopper fitted with silica gel siccative, and a cardboard cover disc.
10, 30 or 50 tablets per pack.

Not all packs sizes may be marketed.

6.6 Special precautions for disposal

At least 100 ml of water should be added, and check to see that the tablet is completely dissolved, which normally takes approximately 3 minutes.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited

11 Boumpoulinas

Nicosia

1060

Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0217

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/03/2009

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25/06/2024