

Product Summary

1. Trade Name of the Medicinal Product

Fluoxetine 20mg Capsules

2. Qualitative and Quantitative Composition

Each capsule contains Fluoxetine 20mg as fluoxetine hydrochloride (22.4mg).
For excipients, see Section 6.1.

3. Pharmaceutical Form

Hard capsule.

Size 3. Capsule cap is light green opaque. Capsule body is standard yellow opaque. Markings are "F20".

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Depression: Fluoxetine is indicated for the treatment of the symptoms of depressive illness, with or without associated anxiety symptoms, especially where sedation is not required.

Obsessive-compulsive disorder.

Bulimia nervosa: Fluoxetine is indicated for the reduction of binge-eating and purging activity.

4.2. Posology and method of administration

For oral administration to adults only.

Depression with or without associated anxiety symptoms - adults and the elderly: A dose of 20 mg/day is recommended.

Obsessive-compulsive disorder: 20mg/day to 60mg/day. A dose of 20mg/day is recommended as the initial dose. Although there may be an increased

potential of side-effects at higher doses, a dose increase may be considered after several weeks if there is no response.

Bulimia nervosa - adults and the elderly: A dose of 60mg/day is recommended.

Children: The use of Fluoxetine in children is not recommended, as safety and efficacy have not been established.

A lower or less frequent dose should be considered in patients with hepatic impairment, concurrent diseases, or who are taking multiple medications (see “4.4 Special Warnings and Precautions for Use” and “4.5 Interactions with other Medicinal products and other forms of Interaction”).

When dosing is stopped, fluoxetine will persist in the body for weeks. This should be borne in mind when starting or stopping treatment. Dosage tapering is unnecessary in most patients.

4.3 Contraindications

Hypersensitivity to fluoxetine or the ingredients of the preparation.

Monoamine oxidase inhibitors: Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI selegiline and the reversible MAOI (RIMA), moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI.

Some cases presented with features resembling serotonin syndrome (which may resemble, and be diagnosed as, neuroleptic malignant syndrome).Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Therefore, fluoxetine should not be used in combination with a non-selective MAOI or RIMA or within 14 days of discontinuing treatment with a MAOI or RIMA.

Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting a MAOI or RIMA.If fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered.

Fluoxetine should not be used in patients with unstable or uncontrolled epilepsy.

The combination of fluoxetine with a reversible MAOI (eg, moclobemide) is not recommended. Treatment with fluoxetine can be initiated the following day after discontinuation of a reversible MAOI.

4.4 Special warnings and precautions for use

Use in children and adolescents under 18 years of age: Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Fluoxetine should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes and it should not be used in other indications. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioural developments (see section 5.3).

In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 4.8). It has not been established whether there is an effect on achieving normal adult height. The possibility of a delay in puberty cannot be ruled out (see sections 5.3 and 4.8). Growth and pubertal development (height, weight, and TANNER staging) should therefore be monitored during and after treatment with fluoxetine. If either is slowed, referral to a paediatrician should be considered.

In paediatric trials, mania and hypomania were commonly reported (see section 4.8). Therefore, regular monitoring for the occurrence of mania/hypomania is recommended. Fluoxetine should be discontinued in any patient entering a manic phase.

It is important that the prescriber discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Fluoxetine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at

greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Akathisia/psychomotor restlessness: The use of fluoxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Withdrawal symptoms seen on discontinuation of SSRI treatment: Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation occurred in approximately 60% of patients in both the fluoxetine and placebo groups. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were severe in nature.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor, and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Fluoxetine should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs.

Rash and allergic reactions - Rash, anaphylactoid events and progressive systemic events, sometimes serious (involving skin, kidney, liver or lung), have been reported. Upon the appearance of rash or of other allergic phenomena for which an alternative aetiology cannot be identified, Fluoxetine should be discontinued.

Seizures - Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures. Fluoxetine should be discontinued in any patients who develop seizures. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy; patients with controlled epilepsy should be carefully monitored. Fluoxetine should be discontinued if there is an increase in seizure frequency.

ECT - there have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment. therefore, caution is advisable.

St John's Wort: An increase in serotonergic effects, such as serotonin syndrome, may occur when selective serotonin reuptake inhibitors and herbal preparations containing St John's Wort (*Hypericum perforatum*) are used together.

On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluoxetine, particularly when given in combination with other serotonergic (among others, L-tryptophan) and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events (characterised by clusters of symptoms, such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes, including confusion, irritability, extreme agitation, progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

Hepatic/renal function - Fluoxetine is extensively metabolised by the liver and excreted in the kidneys. A lower dose, eg, alternate day dosing, is recommended in patients with significant hepatic dysfunction. When given fluoxetine 20mg per day for 2 months, patient with severe renal failure (GFR < 10 ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

Cardiac disease - Clinical experience in acute cardiac disease is limited, therefore caution is advisable. However, the ECG of 312 patients who received fluoxetine in double-blind clinical trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed.

Weight loss - Weight loss may occur in patients taking fluoxetine. Weight loss is usually proportional to baseline body weight.

Diabetes - In patients with diabetes, treatment with fluoxetine may alter glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Haemorrhage - There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRIs. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleeding) have been reported rarely. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) or other drugs that may increase risk of bleeding, as well as in patients with a history of bleeding disorders.

Mania - Fluoxetine should be used with caution in patients with a history of mania/hypomania. Fluoxetine should be discontinued in any patient entering a manic phase.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Monoamine oxidase inhibitors - (see contra-indications).

Not recommended combinations: MAOI-A (see section 4.3).

Combinations requiring precautions for use: MAOI-B (selegiline): Risk of serotonin syndrome. Clinical monitoring is recommended.

Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Lithium and Tryptophan – There have been reports of enhanced effects when SSRIs have been taken with lithium or tryptophan and therefore the concomitant use of Fluoxetine with these drugs be undertaken with caution. When fluoxetine is used in combination with lithium, closer and more frequent clinical monitoring is required.

Drugs predominantly metabolised by CYP2D6 isoenzyme system – Because fluoxetine's metabolism (like tricyclic anti-depressants and other selective serotonin antidepressants) involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with drugs also metabolized by this enzyme system may lead to drug interactions. Concomitant therapy with drugs predominantly metabolised by this isoenzyme, and which have a narrow therapeutic index (such as flecainide, encainide, vinblastine, carbamazepine and tricyclic antidepressants), should be initiated at or adjusted to the low end of their dose range. This will also apply if Fluoxetine has been taken in previous 5 weeks.

Oral anticoagulants - Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is co-administered with oral anticoagulants. As is prudent in concomitant use of oral anticoagulants with many drugs, patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped (see Haemorrhage)

Electroconvulsive therapy (ECT) - There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment, therefore caution is advisable.

Alcohol - The combination of Fluoxetine and alcohol is not advisable. However, in formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol.

Serotonergic drugs - Co-administration with serotonergic drugs (e.g.; tramadol, sumatriptan) may lead to an enhancement of the risk of serotonin syndrome. Use with triptans carries the additional risk of coronary vasoconstriction and hypertension.

St John's Wort - In common with other SSRIs, pharmacodynamic interactions between fluoxetine and herbal remedy, St John's Wort (*Hypericum perforatum*) may occur, which may result in an increase of undesirable effects.

General - The long elimination half-lives of both fluoxetine and norfluoxetine should be borne in mind when considering pharmacodynamic or pharmacokinetic drug interactions (eg, when switching from fluoxetine to other antidepressants).

4.6 Pregnancy and lactation

Pregnancy -. Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Fluoxetine can be used during pregnancy, but caution should be exercised, especially during late pregnancy or just prior to the onset of labour, since the following effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

Lactation - Fluoxetine and its metabolite, norfluoxetine, are known to be excreted in human breast milk. Adverse events have been reported in breast-feeding infants. If treatment with fluoxetine is considered necessary, discontinuation of breast-feeding should be considered; however, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed

Labour and delivery – The effect of fluoxetine on labour and delivery in humans is unknown.

4.7. Effects on ability to drive and use machines

Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgement or skills. Therefore patients should be cautioned that their ability to perform potentially hazardous tasks (*e.g.* driving, operating machinery) may be impaired.

4.8 Undesirable effects

Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

In common with other SSRIs, the following undesirable effects have been seen:

Cardiovascular disorders: Postural hypotension

Cases of QTc prolongation have been reported with fluoxetine therapy.

Disorders of eye: Abnormal vision (eg, blurred vision, mydriasis)

Gastrointestinal Disorders: diarrhoea, nausea; vomiting; dry mouth; diarrhoea; dyspepsia; dysphagia; taste perversion.

General disorders: chills; serotonin syndrome; photosensitivity; and very rarely Erythema Multiforme that could progress to Stevens- Johnson syndrome or Toxic Epidermal Necrolysis (Lyell syndrome); alopecia; yawning; vasodilation; hypersensitivity reactions including pruritus, rash, urticaria, vasculitis, serum sickness-like, angioedema and anaphylactoid reactions. Other haemorrhagic manifestations (eg, gynaecological haemorrhages, gastro-intestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. (See section 4.4, 'Haemorrhage').

Nervous System disorders: headache; sleep abnormalities (e.g., abnormal dreams, insomnia, dizziness; fatigue (e.g., somnolence, drowsiness); anorexia; euphoria; transient abnormal movement (e.g. twitching, ataxia, tremor, myoclonus); rarely psychomotor restlessness / akathisia; seizures.

Very rarely serotonin syndrome, suicidal thoughts and behaviour (these symptoms may be due to the underlying disease). Cases of suicidal ideation and suicidal behaviour have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4).

Hepato-biliary disorders: Abnormal LFT's; very rare cases of idiosyncratic hepatitis.

Musculoskeletal disorders: Arthralgia; myalgia.

Psychiatric disorders: Hallucinations; mania; confusion; agitation; anxiety; impaired concentration and thought process (e.g. depersonalization); panic attacks; nervousness (these symptoms may be due to underlying disease).

Renal & Urinary disorders: Urinary retention; urinary frequency.

Reproductive disorders: Galactorrhoea; sexual dysfunction including ejaculation disorders; anorgasm; priapism.

Skin disorders: Rash; ecchymoses; pruritus; angioedema; sweating.

Disorders of metabolism and nutrition: inappropriate ADH secretion; hyponatraemia; (including serum sodium below 110 mmol/l) has been rarely reported and appears to be reversible when fluoxetine is discontinued. Some

cases were possibly due to syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients, and patients taking diuretics or otherwise volume depleted.

Respiratory system: Pharyngitis, dyspnoea. Pulmonary events (including inflammatory processes of varying histopathology and/or fibrosis) have been reported rarely. Dyspnoea may be the only preceding symptom.

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Children and adolescents: In paediatric clinical trials, suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

The safety of fluoxetine has not been systematically assessed for chronic treatment longer than 19 weeks.

In paediatric clinical trials, manic reactions, including mania and hypomania, were reported (2.6% of fluoxetine-treated patients versus 0% in placebo-controls), leading to discontinuation in the majority of cases. These patients had no prior episodes of hypomania/mania.

After 19 weeks of treatment, paediatric subjects treated with fluoxetine in a clinical trial gained an average of 1.1 cm less in height ($P = 0.004$) and 1.1 kg less in weight ($P = 0.008$) than subjects treated with placebo.

Isolated cases of growth retardation have also been reported from clinical use. Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction have been reported from paediatric clinical use. In paediatric clinical trials, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels.

Withdrawal symptoms seen on discontinuation of fluoxetine treatment: Discontinuation of fluoxetine commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting; however, in some patients they may be severe and/or prolonged (see section 4.4). It is therefore advised that when Fluoxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out. (see section 4.2 and section 4.4)

4.9 Overdose

Cases of overdose of fluoxetine alone usually have a mild course. The fatal dose is not known. The effects will be potentiated by alcohol taken at the same time. Toxicity is also potentiated by tricyclic antidepressants and MAOIs.

Symptoms

Nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare. Cardiac and vital signs monitoring are recommended. No specific antidote is known.

Management

Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

Pharmacological Properties

5.1. Pharmacodynamic Properties

Fluoxetine is chemically unrelated to tricyclic and tetracyclic antidepressant agents. It is a specific serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor, whose specificity is unaltered by its major metabolite. Fluoxetine is a 50:50 mixture of two isomers which have equivalent pharmacological activity in animals. Individuals with reduced P450IID6 isoenzyme activity (3-10% of the normal human population - 'poor metabolisers') were compared to normal metabolisers. The total sum at steady state of the two isomers and their active norfluoxetine metabolites was similar. Thus, net pharmacodynamic activities were essentially the same.

5.2. Pharmacokinetic Properties

Fluoxetine has a half-life of 1 to 3 days after acute administration. The half-life may be prolonged to 4 to 6 days after chronic administration. The active metabolite, norfluoxetine, has a mean half-life of 9.3 days after multiple dosing (range 4 to 16 days). Steady state plasma concentrations are only achieved after continuous dosing for weeks.

When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment.

Plasma concentrations do not appear to increase without limit because, in addition to metabolism by the hepatic cytochrome P450IID6 isoenzyme system, there are non-saturable pathways. Patients receiving fluoxetine for as

long as 3 years exhibited average plasma concentrations, similar to those seen among patients treated for 4 or 5 weeks.

5.3 Preclinical safety data

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.

In a juvenile toxicology study in CD rats, administration of 30mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30mg/kg/day) and females (30mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8-fold (fluoxetine) and 3.6 to 23.2-fold (norfluoxetine) those usually observed in paediatric patients. At 3mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5-fold (fluoxetine) and 0.3 to 2.1-fold (norfluoxetine) those usually achieved in paediatric patients.

A study in juvenile mice has indicated that inhibition of the serotonin transporter prevents the accrual of bone formation. This finding would appear to be supported by clinical findings. The reversibility of this effect has not been established.

Another study in juvenile mice (treated on postnatal days 4 to 21) has demonstrated that inhibition of the serotonin transporter had long-lasting effects on the behaviour of the mice. There is no information on whether the effect was reversible. The clinical relevance of this finding has not been established.

Pharmaceutical Particulars

6.1. List of Excipients

The capsule also contains:
pregelatinised maize starch
colloidal anhydrous silica
magnesium stearate
talc

The capsule shell contains:
quinoline yellow E104
erythrosine E127
indigo carmine E132
titanium dioxide E171
gelatin

The printing ink contains:

shellac (E904)
black iron oxide (E172)
soya lecithin (E322)
antifoam DC 1510

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

2 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

Al/PVC blisters: 28 or 30 capsules/pack
HDPE bottle with snap on cap: 28 or 30 capsules/pack.

6.6. Instruction for Use/Handling

None.

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
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8. MARKETING AUTHORISATION NUMBER

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