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SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

Realiquel 25 (film-coated tablets)

Realiquel 100 (film-coated tablets)

Realiquel 150 (film-coated tablets)

Realiquel 200 (film-coated tablets)

Realiquel 300 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Realiquel 25: Each film-coated tablet contains quetiapine fumarate–equivalent to 25 mg quetiapine.

Realiquel 100: Each film-coated tablet contains quetiapine fumarate–equivalent to 100 mg quetiapine.

Realiquel 150: Each film-coated tablet contains quetiapine fumarate–equivalent to 150 mg quetiapine.

Realiquel 200: Each film-coated tablet contains quetiapine fumarate–equivalent to 200 mg quetiapine.

Realiquel 300: Each film-coated tablet contains quetiapine fumarate–equivalent to 300 mg quetiapine.

Excipients with known effect:

Realiquel 25 contains 7,0 mg lactose monohydrate.

Realiquel 100 contains 28,0 mg lactose monohydrate.

Realiquel 150 contains 42,0 mg lactose monohydrate.

Realiquel 200 contains 56,0 mg lactose monohydrate.

Realiquel 300 contains 84,0 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Realiquel 25: Peach, round, biconvex film-coated tablets with a diameter of 5,7 mm approximately.

Realiquel 100: Yellow, round, biconvex film-coated tablets with a score line on one side and a diameter of 9,1 mm approximately.

Realiquel 150: Pale yellow, round, biconvex film-coated tablets with a diameter of 10,45 mm approximately.

Realiquel 200: White, round, biconvex film-coated tablets with a score line on one side and a diameter of 12,1 mm approximately.

Realiquel 300: White, oblong, biconvex film-coated tablets with a score line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Realiquel is indicated for the treatment of schizophrenia.

Realiquel is also indicated for the treatment of manic episodes associated with a bipolar disorder. Safety and efficacy beyond 12 weeks has not been demonstrated.

4.2 Posology and method of administration

Realiquel should be administered twice daily, with or without food.

Adults:

The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

From Day 4 onwards, the dose should be titrated to the effective dose range of 300 to 450 mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted in some patients within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder, the total daily dose for the first 4 days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

The dose may be adjusted depending on the clinical response and tolerability of the individual patient, within the range of 200 – 800 mg/day. The usual effective dose is in the range of 400 – 800 mg/day.

Elderly:

Realiquel should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on **Realiquel** 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Renal and hepatic impairment:

The oral clearance of **Realiquel** is reduced by approximately 25 % in patients with renal or hepatic impairment. **Realiquel** is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment.

Patients with renal or hepatic impairment should be started on **Realiquel** 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg to an effective dose.

4.3 Contraindications

- **Realiquel** is contraindicated in patients who are hypersensitive to quetiapine or any of the ingredients of **Realiquel**.
- Pregnancy and lactation, as safety has not been demonstrated.

- Safety and efficacy in children and adolescents have not been demonstrated.
- Advanced liver and renal function impairment, as safety has not been demonstrated.

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression in bipolar disorder 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.

In addition, medical practitioners should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which quetiapine is prescribed, can also be associated with an increased risk of suicide related events. 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.

Close supervision of patients and in particular those at high risk should accompany medicine 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.

Metabolic risk

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see ***Hyperglycaemia and diabetes mellitus***), patients' metabolic parameters

should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment.

Worsening in these parameters should be managed as clinically appropriate.

Extrapyramidal symptoms

Realiquel has been associated with an increased incidence of extrapyramidal symptoms.

The use of **Realiquel** 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.

Tardive dyskinesia

There is a potential for **Realiquel** to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, discontinuation of **Realiquel** should be considered.

The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment.

Somnolence

Realiquel treatment has been associated with somnolence and related symptoms, such as sedation. Somnolence may occur, usually during the first 2 weeks of treatment and generally resolves with the continued administration of **Realiquel**.

Orthostatic hypotension

Realiquel treatment has been associated with orthostatic hypotension and related dizziness which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population.

Realiquel should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

Sleep apnoea syndrome

Sleep apnoea syndrome has been reported in patients using **Realiquel**. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, **Realiquel** should be used with caution.

Seizures

Caution is recommended when treating patients with a history of seizures.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with **Realiquel** treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, **Realiquel** should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis

Severe cases of neutropenia (neutrophil count < 0,5 x 10^9/litre) have been reported with **Realiquel**. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with **Realiquel**. There is no apparent dose relationship. Some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count and history of medicine induced neutropenia.

However, some cases have occurred in patients without pre-existing risk factors.

Realiquel should be discontinued in patients with a neutrophil count < 1,0 x 10^9/litre. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 x 10^9/litre).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy or sore throat) at any time during **Realiquel** therapy. Such patients should have a white blood cell count and an absolute neutrophil count performed promptly, especially in the absence of predisposing factors.

Anti-cholinergic (muscarinic) effects

Realiquel should be used with caution in patients receiving medicines having anti-cholinergic (muscarinic) effects. **Realiquel** should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma.

Weight

Weight gain has been reported in patients who have been treated with **Realiquel**, and should be monitored and managed as clinically appropriate.

Weight gain occurs predominantly during the early weeks of treatment.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with **Realiquel**.

Patients with an established diagnosis of diabetes mellitus who are started on **Realiquel**, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg. obesity, family history of diabetes) who are starting treatment with **Realiquel**, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness.

Patients who develop symptoms of hyperglycaemia during treatment with **Realiquel,** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **Realiquel,** was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

Lipids

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed with **Realiquel**. Lipid changes should be managed as clinically appropriate.

QT prolongation

QT prolongation has been reported with quetiapine at the therapeutic doses. Caution should be exercised when **Realiquel** is prescribed in patients with cardiovascular disease or family history of QT prolongation.

Also, caution should be exercised when **Realiquel** is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported. Treatment with **Realiquel** should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Withdrawal

Acute withdrawal symptoms such as nausea, headache, diarrhoea, dizziness, irritability, vomiting and insomnia have been described after abrupt cessation of **Realiquel**. Gradual withdrawal over a period of at least one to two weeks is advisable.

Elderly patients with dementia-related psychosis

Realiquel is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. **Realiquel** should be used with caution in patients with risk factors for stroke.

Where the use of antipsychotics in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, oversedation and complications associated with hyperglycemia.

Dysphagia

Dysphagia has been reported with quetiapine. **Realiquel** should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with **Realiquel**. Patients with intestinal obstruction/ileus should be managed with close monitoring.

Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with **Realiquel** and preventive measures undertaken.

Pancreatitis

Pancreatitis has been reported in patients treated with **Realiquel**.

Misuse and abuse

Cases of misuse and abuse have been reported. Caution may be needed when prescribing **Realiquel** to patients with a history of alcohol or drug abuse.

Lactose

Realiquel tablets contain lactose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **Realiquel**.

4.5 Interactions with other medicinal products and other forms of interactions

Given the primary central nervous system effects of quetiapine, **Realiquel** should be used with caution in combination with other centrally acting medicines and alcohol.

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of **Realiquel**. The pharmacokinetics of **Realiquel** was not altered following co-administration with cimetidine a known P450 enzyme inhibitor. The pharmacokinetics of **Realiquel** was not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).
In an interaction study in healthy volunteers, co-administration of **Realiquel** (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. Due to the potential for an interaction of similar magnitude in a clinical setting, the dosage of **Realiquel** should be reduced during concomitant use of **Realiquel** and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors). It is also not recommended to take **Realiquel** with grapefruit juice.

The co-administration of **Realiquel** with strong hepatic enzyme inducers such as carbamazepine or phenytoin and other hepatic enzyme inducers (e.g., barbiturates, rifampicin etc.) substantially decreases **Realiquel** plasma concentrations, which could affect the efficacy

of **Realiquel** therapy. As a consequence of this interaction, in each patient, consideration for a higher dose of **Realiquel,** depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of **Realiquel** is 750 mg/day for the treatment of schizophrenia, and 800 mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit-risk assessment for an individual patient. Increased doses of **Realiquel** may be required to maintain control of psychotic symptoms in patients where **Realiquel** and hepatic enzyme inducers are co-administered. The dose of **Realiquel** may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

The pharmacokinetics of **Realiquel** was not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of **Realiquel** and thioridazine caused increases in clearance of **Realiquel**.

The pharmacokinetics of lithium was not altered when co-administered with **Realiquel**. A study showed an increase in side effects such as somnolence, extrapyramidal effects and weight gain.

The pharmacokinetics of sodium valproate and **Realiquel** were not altered to a clinically relevant extent when co-administered.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

Caution should be exercised when **Realiquel** is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval.

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken **Realiquel**. Confirmation of screening results by an appropriate chromatographic technique is recommended.

Realiquel did not induce the hepatic enzyme systems involved in the metabolism of antipyrine.

4.6 Fertility , pregnancy and lactation

The safety of **Realiquel** in pregnant and lactating women has not been established (see section 4.3).

Pregnancy

Realiquel is contraindicated in lactation.

Lactation

Realiquel is contraindicated in lactation

Fertility

The effects of quetiapine on human fertility have not been assessed.

4.7 Effects on ability to drive and use machines

Realiquel may cause somnolence which may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) with **Realiquel** (≥ 10 %) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

The incidences of side effects associated with **Realiquel** therapy, are given below:

Blood and the lymphatic system disorders

Frequent: Decreased haemoglobin, leucopenia, decreased neutrophil count, increased eosinophils.

Less frequent: Neutropenia, thrombocytopenia, anaemia, decreased platelet count, agranulocytosis.

Immune system disorders

Less frequent: Hypersensitivity (angioedema, anaphylaxis, urticaria/rash).

Endocrine disorders

Frequent: Hyperprolactinaemia, decreases in total T4, decreases in free T4, decreases in total T3, increases in TSH.

Less frequent: Decreases in free T3, hypothyroidism, inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Frequent: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, increased appetite, blood glucose increased to hyperglycaemic levels.

Less frequent: Hyponatraemia, diabetes mellitus, exacerbation of pre-existing diabetes, metabolic syndrome.

Psychiatric disorders

Frequent: Abnormal dreams and nightmares, suicidal ideation and suicidal behaviour.

Less frequent: Somnambulism and related reactions such as sleep talking and sleep related eating disorder.

Nervous system disorders

Frequent: Headache, somnolence, dizziness, anxiety, extrapyramidal symptoms (akathisia, cogwheel rigidity, hypertonia, hypokinesia, neck rigidity and tremor), dysarthria.

Less frequent: Seizure, restless leg syndrome, tardive dyskinesia, syncope.

Eye disorders

Frequent: Dry eyes, asymptomatic changes in lenses of the eyes with long term use, blurred vision.

Ear and labyrinth disorders

Less frequent: Ear pain.

***Cardiac disorders*:**

Frequent: Tachycardia, palpitations.

Less frequent: QT prolongation, bradycardia, chest pain.

Vascular disorders

Frequent: Orthostatic hypotension (associated with dizziness, tachycardia and syncope in some patients).

Less frequent: Venous thromboembolism.

Frequency unknown: Stroke.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea.

Less frequent: Rhinitis.

Gastro-intestinal disorders

Frequent: Constipation, dry mouth, dyspepsia, vomiting.

Less frequent: Abdominal pain, diarrhoea, dysphagia, pancreatitis, intestinal obstruction/ileus.

Hepato-biliary disorders

Frequent: Elevations in serum alanine aminotransferase (ALT), elevations in gamma-GT levels.

Less frequent: Elevations in serum aspartate aminotransferase (AST), jaundice, hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: Angioedema, Stevens-Johnson syndrome.

Frequency unknown: Toxic epidermal necrolysis, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Musculoskeletal, connective tissue and bone disorders

Less frequent: Myalgia, back pain, rhabdomyolysis.

Renal and urinary disorders

Less frequent: Urinary tract infection, urinary retention.

Pregnancy, puerperium and perinatal conditions

Frequency unknown: Substance withdrawal syndrome neonatal.

Reproductive system and breast disorders

Less frequent: Sexual dysfunction, priapism, galactorrhoea, breast swelling, menstrual disorder.

General disorders

Frequent: Withdrawal symptoms, mild asthenia, peripheral oedema, irritability, pyrexia.

Less frequent: Neuroleptic malignant syndrome, hypothermia.

Investigations

Less frequent: Elevations in blood creatine phosphokinase.

Elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in patients administered **Realiquel.** These elevations were usually reversible on continued **Realiquel** treatment.

Realiquel treatment was associated with dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first 2 to 4 weeks of **Realiquel** treatment, with no further reduction during long-term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of **Realiquel** treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. Smaller decreases in total T_3 and reverse T_3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with any indication that **Realiquel** causes clinically relevant hypothyroidism.

4.9 Overdose

In clinical trials, experience with **Realiquel** in overdosage is limited.

In general, reported signs and symptoms were those resulting from an exacerbation of **Realiquel**'s known pharmacological effects, i.e. drowsiness, sedation, tachycardia and hypotension.

There is no specific antidote to **Realiquel**. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 2.6.5 Central nervous system depressants: Miscellaneous structures

Pharmacotherapeutic group: Antipsychotics; diazepines, oxazepines and thiazepines. ATC code: N05A H04

5.1 Pharmacodynamic properties

Quetiapine is an atypical antipsychotic medicine, which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin ($5HT_2$) receptors in the brain than it does for dopamine D_1 and D_2 receptors in the brain. Quetiapine also has high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic alpha-2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors. In animal models, quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance.

Quetiapine does not produce sustained elevations of prolactin in man.

Quetiapine, when given twice a day, maintains $5HT_2$ and D_2 receptor occupancy for up to 12 hours after dosing.

5.2 Pharmacokinetic properties

Absorption

Quetiapine is absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significant affected by administration with food.

The principle human plasma metabolites do not have significant pharmacological activity.

Distribution

Quetiapine is approximately 65 % - 83 % bound to plasma proteins.

Biotransformation

Quetiapine is extensively metabolised with the parent compound accounting for less than 5 % of unchanged quetiapine in the urine or faeces, following the administration of radio-labelled quetiapine. *In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine.

Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

Quetiapine and several of its metabolites were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities, but only at concentrations at least 10 to 50 fold higher than those observed in the usual effective dose range of 300 to 450 mg/day in humans.

Elimination

The elimination half-life of quetiapine is approximately 7 hours.

Gender

The pharmacokinetics of quetiapine are variable, but do not differ significantly between men and women.

Elderly

The mean clearance of quetiapine in the elderly is approximately 30 % to 50 % lower than that seen in adults aged 18 to 65 years.

Renal and hepatic impairment

The mean plasma clearance of quetiapine was reduced by approximately 25 % in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73 m^2) and in

subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other ingredients are hypromellose, calcium hydrogen phosphate dihydrate, lactose monohydrate, maize starch, sodium starch glycollate, magnesium stearate, microcrystalline cellulose, talc, silica colloidal anhydrous and film-coating colourants.

Realiquel 25 contains opadry pink colourant (iron oxide red, iron oxide yellow, hypromellose, titanium dioxide, macrogol and FD+C Yellow #6/Sunset yellow FCF Aluminium lake).

Realiquel 100 contains opadry yellow colourant (iron oxide yellow, hypromellose, titanium dioxide, magrogol).

Realiquel 150 contains opadry yellow and opadry white colourants (iron oxide yellow, hypromellose, titanium dioxide, magrogol, hydroxyl cellulose and talc).

Realiquel 200 and **300** contains opadry white colourant (hydroxypropyl cellulose, hypromellose, titanium dioxide and talc).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 ºC. Keep blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Realiquel film-coated tablets are supplied in opaque PVC/silver aluminium blister packs of 28 or 30 tablets.

Realiquel 25: Packs of 28 or 30 tablets

Realiquel 100: Packs of 28 or 30 tablets

Realiquel 150: Packs of 28 or 30 tablets

Realiquel 200: Packs of 28 or 30 tablets

Realiquel 300: Packs of 28 or 30 tablets

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Smart Pharmaceuticals (Pty) Ltd

247 Voortrekker Road

Kraaifontein

Cape Town, 7570

8. REGISTRATION NUMBERS

Realiquel 25: (awaiting)

Realiquel 100: (awaiting)

Realiquel 150: (awaiting)

Realiquel 200: (awaiting)

Realiquel 300: (awaiting)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: Await

10. DATE OF REVISION OF THE TEXT