SCHEDULING STATUS S5

PROPRIETARY NAME AND DOSAGE FORM

DOPAQUEL 25 (film-coated tablet)

DOPAQUEL 100 (film-coated tablet)

DOPAQUEL 200 (film-coated tablet)

DOPAQUEL 300 (film-coated tablet)

COMPOSITION

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

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

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

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

Other ingredients are colloidal silicon dioxide, dibasic calcium phosphate dihydrate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. The 25, 200 and 300 mg film-coated tablets contain Opadry® white (hypromellose, macrogol and titanium dioxide). The 100 mg film-coated tablets contain Opadry® yellow (hypromellose, iron oxide yellow, macrogol and titanium dioxide).

Contains sugar: Lactose

PHARMACOLOGICAL CLASSIFICATION

A. 2.6.5 Central nervous system depressants: Miscellaneous structures.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Quetiapine is an atypical antipsychotic agent 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. Quetiapine does not produce sustained elevations in prolactin in man.

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

Pharmacokinetic properties

After oral administration quetiapine is absorbed and extensively metabolised. The principal human plasma metabolites do not have significant pharmacological activity. The bioavailability of quetiapine is not significantly affected by administration with food. The elimination half-life of quetiapine is approximately 7 hours. Quetiapine is approximately 65 % - 83 % bound to plasma proteins.

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

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

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.

Quetiapine is extensively metabolised with parent compound accounting for less than 5 % of unchanged medicine related material in the urine or faeces, following the administration of radio-labelled quetiapine. Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome

P450 mediated metabolism of quetiapine.

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.

INDICATIONS

DOPAQUEL is indicated for the treatment of schizophrenia.

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

CONTRAINDICATIONS

DOPAQUEL is contraindicated in:

Patients who are hypersensitive to quetiapine or to any component of this product.

Pregnancy and lactation, as safety has not been demonstrated.

Advanced liver and renal function impairment, as safety has not been demonstrated.

Children and adolescents below the age of 18 years as safety and efficacy have not been demonstrated.

Co-administration with cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin and clarithromycin, is contraindicated (see **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

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 **DOPAQUEL** treatment, due to the known risk factors for the disease being

treated.

Other psychiatric conditions for which **DOPAQUEL** 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 suicidal 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 ideation and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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 **DOPAQUEL**. Patients with an established diagnosis of diabetes mellitus who are started on **DOPAQUEL** should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with **DOPAQUEL** should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with **DOPAQUEL** should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when **DOPAQUEL** was discontinued, however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Metabolic risk

Given the 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

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

The use of **DOPAQUEL** 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 **DOPAQUEL** to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, discontinuation of **DOPAQUEL** should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment.

Somnolence

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

Orthostatic hypotension

DOPAQUEL 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.

DOPAQUEL 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.

Seizures

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

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with **DOPAQUEL** treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, **DOPAQUEL** 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 **DOPAQUEL**. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with **DOPAQUEL**. 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.

DOPAQUEL 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 fever or infection, 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 **DOPAQUEL** therapy. Such patients should have a white blood cell count and an absolute neutrophil count performed promptly, especially in the absence of predisposing factors.

Weight

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

Weight gain occurs predominantly during the early weeks of treatment.

Lipids

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

QT prolongation

QT prolongation has been reported with quetiapine at the therapeutic doses and in overdose.

Caution should be exercised when **DOPAQUEL** is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when **DOPAQUEL** is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e. the elderly, 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 **DOPAQUEL** should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Elderly patients with dementia

DOPAQUEL is not indicated for use in elderly patients with dementia exhibiting behavioural disturbances.

An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics such as **DOPAQUEL**. An increased risk cannot be excluded for other patient populations.

Elderly patients

Where the use of **DOPAQUEL** 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, over-sedation and complications associated with hyperglycaemia.

Dysphagia

Dysphagia has been reported with quetiapine. **DOPAQUEL** 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 **DOPAQUEL**. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

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 **DOPAQUEL** and preventive measures undertaken.

Withdrawal reactions

Acute withdrawal symptoms including nausea, vomiting, headache, diarrhoea, dizziness, irritability and insomnia have been described after abrupt cessation of **DOPAQUEL**. Recurrence of psychotic

symptoms may also occur and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesias) have been reported. Gradual withdrawal over a period of at least one to two weeks is advisable.

Effects on ability to drive and use machines

DOPAQUEL 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.

Lactose

DOPAQUEL film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

INTERACTIONS

Concomitant use of **DOPAQUEL** with:

Other centrally acting medicines or alcohol - **DOPAQUEL** may enhance the primary central nervous system effects of other CNS depressants, including alcohol.

The pharmacokinetics of lithium are not altered when co-administered with quetiapine as in **DOPAQUEL**.

DOPAQUEL should be used with caution in patients also receiving antihypertensives or medicines known to cause electrolyte imbalance or to prolong the QTc interval.

DOPAQUEL may antagonise the actions of dopaminergics, such as levodopa.

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

The pharmacokinetics of **DOPAQUEL** are not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of **DOPAQUEL** and thioridazine has caused increases in clearance of quetiapine as in **DOPAQUEL**.

Quetiapine as in **DOPAQUEL** does not induce the hepatic enzyme systems involved in the metabolism of antipyrine.

Hepatic enzyme inducers - The co-administration of carbamazepine significantly increases the

clearance of **DOPAQUEL**. This increase in clearance significantly reduces systemic **DOPAQUEL** exposure. As a consequence of this interaction, lower plasma concentrations can occur, and hence in each patient, consideration for a higher dose of **DOPAQUEL**, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of **DOPAQUEL** 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.

Co-administration of **DOPAQUEL** with another microsomal enzyme inducer, phenytoin, also caused increases in clearance of **DOPAQUEL**. Increased doses of **DOPAQUEL** may be required to maintain control of psychotic symptoms in patients co-administered with **DOPAQUEL** and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of **DOPAQUEL** may need to be reduced when phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 inhibitors - CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of **DOPAQUEL**. The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine as in **DOPAQUEL** were also not significantly altered following co-administration with the anti-depressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

However, co-administration of ketoconazole may result in a significant (5-fold) increase in the AUC of quetiapine as in **DOPAQUEL**. On the basis of this, concomitant use of **DOPAQUEL** and potent CYP3A4 inhibitors (such as HIV protease inhibitors, azole antifungals and macrolide antibiotics), is contraindicated (see **CONTRAINDICATIONS**). It is also not recommended to consume grapefruit juice while on **DOPAQUEL** therapy as serum concentration may be increased.

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

PREGNANCY AND LACTATION

DOPAQUEL is contra-indicated during pregnancy and lactation, as safety has not been demonstrated (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

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

Adults

For the treatment of schizophrenia the total daily dose for the first 4 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

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

Renal and hepatic impairment

The clearance of **DOPAQUEL** is reduced by approximately 25 % in patients with renal or hepatic impairment. **DOPAQUEL** 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 **DOPAQUEL** 25 mg/day. The dose

should be increased daily in increments of 25 mg to 50 mg, to an effective dose.

SIDE-EFFECTS

The most commonly reported adverse drug reactions (ADRs) with **DOPAQUEL** are somnolence, dizziness, dry mouth, asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia. Weight gain, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema have been associated with **DOPAQUEL**.

Blood and the lymphatic system disorders

Frequent: Leucopenia

Less frequent: Eosinophilia, neutropenia, thrombocytopenia, agranulocytosis, anaemia

Immune system disorders

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

Metabolism and nutrition disorders

Less frequent: Hyperglycaemia, diabetes mellitus (or exacerbation of pre-existing diabetes)

Endocrine disorders

Frequent: Hyperprolactinaemia

Less frequent: Hypothyroidism, inappropriate antidiuretic hormone secretion

Psychiatric disorders

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

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

Nervous system disorders

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

Less frequent: Seizures, neuroleptic malignant syndrome (See **WARNINGS AND SPECIAL PRECAUTIONS**), tardive dyskinesia, restless legs syndrome

Eye disorders

Frequency not known: 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: QTc prolongation, chest pain, bradycardia

Vascular disorders

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

Less frequent: Venous thromboembolism

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea, rhinitis

Gastrointestinal disorders

Frequent: Dry mouth, constipation, dyspepsia, vomiting

Less frequent: Diarrhoea, abdominal pain, dysphagia, pancreatitis, intestinal obstruction/ileus

Hepato-biliary disorders

Less frequent: Jaundice, hepatitis

Skin and subcutaneous tissue disorders

Less frequent: Angioedema, Stevens-Johnson syndrome

Frequency not known: Toxic epidermal necrolysis, erythema multiforme

Musculoskeletal, connective tissue and bone disorders

Less frequent: Myalgia, rhabdomyolysis, back pain

Renal and urinary disorders

Less frequent: Urinary tract infection, urinary retention

Reproductive system and breast disorders

Less frequent: Priapism, galactorrhoea, sexual dysfunction, breast swelling, menstrual disorder

General disorders and administration site conditions

Frequent: Asthenia, peripheral oedema, withdrawal symptoms (see **WARNINGS AND SPECIAL**

PRECAUTIONS)

Less frequent: Fever, hypothermia

Investigations

Frequent: Weight gain, elevations in serum transaminases (ALT, AST), decreases in total T_4, decreases in free T_4, decreases in total T_3, increases in TSH, decreased haemoglobin, decreased neutrophil count

Less frequent: Elevations in gamma-GT levels, elevations in non-fasting triglyceride levels, elevations in total cholesterol, decreases in free T_3, platelet count decreased, elevations in blood creatine phosphokinase

DOPAQUEL was associated with dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total T_4 and free T_4 was maximal within the first 2 to 4 weeks of **DOPAQUEL** 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 **DOPAQUEL** treatment has been 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 **DOPAQUEL** causes clinically relevant hypothyroidism.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In general, reported signs and symptoms were those resulting from an exaggeration of the pharmacological effects i.e. drowsiness, sedation, tachycardia and hypotension.

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

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

IDENTIFICATION

DOPAQUEL 25: White, round, biconvex, film-coated tablets debossed with 'R' on one side and '1' on the other side.

DOPAQUEL 100: Yellow, round, biconvex, film-coated tablets debossed with 'R' on one side and '3' on the other side.

DOPAQUEL 200: White, round, biconvex, film-coated tablets debossed with 'R' on one side and '5' on the other side.

DOPAQUEL 300: White, modified capsule shaped, biconvex, film-coated tablets debossed with 'R' on one side and '6' on the other side.

PRESENTATION

DOPAQUEL 25: 30, 60, 100 or 500 film-coated tablets in white HDPE containers. Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.

DOPAQUEL 100: 30, 60, 90, 100 or 500 film-coated tablets in white HDPE containers. Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.

DOPAQUEL 200: 30, 60, 100 or 500 film-coated tablets in white HDPE containers. Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.

DOPAQUEL 300: 30, 60, 100 or 500 film-coated tablets in white HDPE containers. Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep the HDPE containers tightly closed.

Keep tablets in the original container.

KEEP OUT OF THE REACH OF CHILDREN

REGISTRATION NUMBERS

DOPAQUEL 25: 43/2.6.5/0429

DOPAQUEL 100: 43/2.6.5/0430

DOPAQUEL 200: 43/2.6.5/0431

DOPAQUEL 300: 43/2.6.5/0432

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PACKAGE INSERT

02 June 2017