SCHEDULING STATUS:

Schedule 4

PROPRIETARY NAME AND DOSAGE FORM:

AZILECT 1 mg TABLETS

COMPOSITION:

Each tablet contains 1,56 mg rasagiline mesylate equivalent to 1 mg rasagiline base.

PHARMACOLOGICAL CLASSIFICATION:

A 5.4.1 Anti-Parkinsonism preparations.

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Rasagiline was shown to be a potent, irreversible MAO-B selective inhibitor, which may cause an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.

1-Aminoindan is an active major metabolite and it is not a MAO-B inhibitor.

Pharmacokinetics

Absorption: Rasagiline is rapidly absorbed, reaching peak plasma concentration (C_{max}) in approximately 0.5 hours. The absolute bioavailability of a single rasagiline dose is about 36%**.**

Food does not affect the T_{max} of rasagiline, although C_{max} and exposure (AUC) are decreased by approximately 60% and 20%, respectively, when the medicinal product is taken with a high fat meal. Because AUC is not substantially affected, rasagiline can be administered with or without food.

Distribution: The mean volume of distribution following a single intravenous dose of rasagiline is 243 l. Plasma protein binding following a single oral dose of ^{14}C-labelled rasagiline is approximately 60 to 70%.

Metabolism: Rasagiline undergoes almost complete biotransformation in the liver prior to excretion. The metabolism of rasagiline proceeds through two main pathways: N-dealkylation and/or hydroxylation to yield: 1-Aminoindan, 3-hydroxy-N-propargyl-1 aminoindan and 3-hydroxy-1-aminoindan. *In vitro* experiments indicate that both routes of rasagiline metabolism are dependent on cytochrome P450 system, with CYP1A2 being the major iso-enzyme involved in rasagiline metabolism. Conjugation of rasagiline and its metabolites was also found to be a major elimination pathway to yield glucuronides.

Excretion: After oral administration of ^{14}C-labelled rasagiline, elimination occurred primarily via urine (62.6%) and secondarily via faeces (21.8%), with a total recovery of 84.4% of the dose over a period of 38 days. Less than 1% of rasagiline is excreted as unchanged product in urine.

Linearity/non-linearity: Rasagiline pharmacokinetics are linear with dose over the range of 0,5 - 2 mg. Its terminal half-life is 0.6-2 hours.

Characteristics in patients

Patients with hepatic impairment*:* In subjects with mild hepatic impairment (Child Pugh score 5 – 6), AUC and C_{max} were increased by 80% and 38%, respectively. In subjects with moderate hepatic

impairment (Child Pugh B), AUC and C_{max} were increased by 568% and 83%, respectively (see Contra-indications and Special Precautions).

Patients with renal impairment*:* Rasagiline's pharmacokinetics characteristics in subjects with mild (CLcr 50-80 ml/min) and moderate (CLcr 30-49 ml/min) renal impairment were similar to healthy subjects.

INDICATIONS:

AZILECT is indicated for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

CONTRA-INDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.

Concomitant treatment with other monoamine oxidase (MAO) inhibitors or pethidine (see Interactions). At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with MAO inhibitors or pethidine.

AZILECT is contraindicated in patients with moderate or severe hepatic insufficiency (Child Pugh B and C).

WARNINGS:

The concomitant use of AZILECT and fluoxetine or fluvoxamine should be avoided (see Interactions). At least five weeks should elapse between discontinuation of fluoxetine and initiation of treatment with AZILECT**.** At least 14 days should elapse between discontinuation of AZILECT and initiation of treatment with fluoxetine or fluvoxamine.

The concomitant use of AZILECT and dextromethorphan or sympathomimetics, such as those present in nasal and oral decongestants or cold medications containing ephedrine or pseudoephedrine, is not recommended (see Interactions).

INTERACTIONS:

There are a number of known interactions between non selective MAO inhibitors and other medicinal products.

AZILECT should not be administered along with other MAO inhibitors as there may be a risk of non-selective MAO inhibition that may lead to hypertensive crises (see Contra-Indications).

Serious adverse reactions have been reported with the concomitant use of pethidine and MAO inhibitors as well as with another selective MAO-B inhibitor. The concomitant administration of AZILECT and pethidine is contraindicated (see Contra-Indications).

The concomitant use of AZILECT and fluoxetine or fluvoxamine should be avoided (see Warnings).

With MAO inhibitors as well as with another selective MAO-B inhibitor there have been reports of drug interactions with the concomitant use of sympathomimetic medicinal products. Therefore, in view of the MAO inhibitory activity of AZILECT, concomitant administration of AZILECT and sympathomimetics such as those present in nasal and oral decongestants or cold medications containing ephedrine or pseudoephedrine, is not recommended (see Warnings).

There have been reports of drug interactions with the concomitant use of dextromethorphan and non selective MAO inhibitors. Therefore, in view of the MAO inhibitory activity of AZILECT, the concomitant administration of AZILECT and dextromethorphan is not recommended (see Warnings).

Serious adverse reactions have been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs), tricyclic, tetracylic antidepressants and MAO inhibitors as well as with another selective MAO-B inhibitor. Therefore, in view of the MAO inhibitory activity of AZILECT, antidepressants should be administered with caution.

In Parkinson's disease patients receiving chronic levodopa treatment as adjunct therapy, there was no clinically significant effect of levodopa treatment on AZILECT clearance.

In vitro metabolism studies have indicated that cytochrome P450 1A2 (CYP1A2) is the major enzyme responsible for the metabolism of AZILECT. Co-administration of AZILECT and ciprofloxacin (an inhibitor of CYP1A2) increased the AUC of AZILECT by 83%. Co-administration of AZILECT and theophylline (a substrate of CYP1A2) did not affect the pharmacokinetics of either product. Thus, potent CYP1A2 inhibitors may alter AZILECT plasma levels and should be administered with caution.

There is a risk that the plasma levels of AZILECT in smoking patients could be decreased, due to induction of the metabolising enzyme CYP1A2.

In vitro studies showed that AZILECT at a concentration of 1 µg/ml (equivalent to a level that is 160 times the average C_{max} ~ 5.9-8.5 ng/ml in Parkinson's disease patients after 1 mg AZILECT multiple dosing), did not inhibit cytochrome P450 isoenzymes, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A. These results indicate that AZILECT's therapeutic concentrations are unlikely to cause any clinically significant interference with substrates of these enzymes.

Concomitant administration of AZILECT and entacapone increased AZILECT oral clearance by 28%.

Tyramine/AZILECT interaction: Results of four tyramine challenge studies (in volunteers and PD patients), together with results of home monitoring of blood pressure after meals (of 464 patients treated with 0,5 or 1 mg/day of AZILECT or placebo as adjunct therapy to levodopa for six months without tyramine restrictions), and the fact that there were no reports of tyramine/AZILECT interaction in clinical studies conducted without tyramine restriction, indicate that AZILECT can be used safely without dietary tyramine restrictions.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been demonstrated.

DOSAGE AND DIRECTIONS FOR USE:

AZILECT is administered orally, at a dose of 1 mg once daily with or without levodopa.

It may be taken with or without food.

Elderly: No change in dosage is required for elderly patients.

Children and adolescents (<18 years): Not recommended as the safety and efficacy have not been established in this population.

Patients with hepatic impairment: AZILECT use in patients with moderate or severe hepatic impairment is contraindicated (see Contra-Indications). Caution should be used when initiating treatment with AZILECT in patients with mild hepatic insufficiency. In case patients progress from mild to moderate hepatic impairment AZILECT should be stopped (see Special Precautions).

Patients with renal impairment: No change in dosage is required for renal impairment.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

In the AZILECT clinical program overall 1360 patients were treated with AZILECT for 2017 patient years. In the double blind placebo controlled studies 529 patients were treated with AZILECT 1 mg/day for 212 patient years and 539 patients received placebo for 213 patient years.

Monotherapy

The list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies, in patients receiving 1 mg/day AZILECT (AZILECT group n=149, placebo group n=151).

Adverse reactions are ranked under headings of frequency using the following conventions: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000) including isolated reports.

Body as a Whole:

very common: headache.

common: flu syndrome, malaise, neck pain, allergic reaction, fever.

Cardiovascular System:

common: angina pectoris.

uncommon: cerebrovascular accident, myocardial infarct.

Digestive System:

common: dyspepsia, anorexia.

Haemic and Lymphatic System:

common: leucopenia.

Musculoskeletal System:

common: arthralgia, arthritis.

Nervous System:

common: depression, vertigo.

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Respiratory System:

common: rhinitis.

Special Senses:

common: conjunctivitis.

Skin and Appendages:

common: contact dermatitis, vesiculobullous rash, skin carcinoma.

Urogenital System:

common: urinary urgency.

Adjunct Therapy

The list below includes adverse reactions which were reported with a higher incidence in placebo-controlled studies in patients receiving 1 mg/day AZILECT (AZILECT group n=380, placebo group n=388).

Adverse reactions are ranked under headings of frequency using the following conventions: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000) including isolated reports.

Body as a Whole:

common: abdominal pain, accidental injury (primarily falls), neck pain.

Cardiovascular System:

common: postural hypotension.

uncommon: angina pectoris, cerebrovascular accident.

Digestive System:

common: constipation, vomiting, anorexia, dry mouth.

Musculoskeletal System:

common: arthralgia, tenosynovitis.

Metabolic and Nutritional:

common: weight loss.

Nervous System:

very common: dyskinesia.

common: dystonia, abnormal dreams, ataxia.

Skin and Appendages:

common: rash.

uncommon: skin melanoma.

Other important adverse events that were reported in clinical studies with AZILECT (other dose or in studies without placebo control), that occurred in two patients each, were rhabdomyolysis (both cases were following fall and prolonged immobilization) and inappropriate antidiuretic hormone (ADH) secretion. The complicated nature of these cases makes it impossible to determine what role, if any, AZILECT played in their pathogenesis.

Post Marketing Data

In post marketing experience symptoms of hallucinations and confusion have been observed in Parkinson's disease patients treated with AZILECT.

Special Precautions:

During the clinical development program, the occurrence of cases of melanoma prompted the consideration of a possible association with AZILECT. The data collected suggests that Parkinson's disease, and not any medicine in particular, is associated with a higher risk of skin cancer (not exclusively melanoma). Any suspicious skin lesion should be evaluated by a specialist.

Caution should be used when initiating treatment with AZILECT in patients with mild hepatic insufficiency. AZILECT use in patients with moderate or severe hepatic impairment is contraindicated. In case patients progress from mild to moderate hepatic impairment, AZILECT should be stopped.

Effects on ability to drive or use machines

No studies on the effects on the ability to drive and use machines have been performed.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No cases of overdose have been reported in clinical studies.

Theoretically, overdose can cause significant inhibition of both MAO-A and MAO-B. In a single-dose study healthy volunteers received 20 mg/day and in a ten-day study healthy volunteers received 10 mg/day. Adverse events were mild or moderate and not related to AZILECT treatment. In a dose escalation study in patients on chronic levodopa therapy treated with 10 mg/day of AZILECT, there were reports of cardiovascular undesirable effects (including hypertension and postural hypotension) which resolved following treatment discontinuation. These symptoms may resemble those observed with non-selective MAO inhibitors.

There is no specific antidote. In case of overdose, patients should be monitored, and the appropriate symptomatic and supportive therapy instituted.

IDENTIFICATION:

White to off-white, round, flat, bevelled tablet; debossed "GIL 1" on one side and plain on the other side.

PRESENTATION:

Blisters: Aluminium/aluminium blister packs of 28 tablets.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in the original package.

Do not remove blisters from outer carton until required for use.

Keep out of reach of children.

REGISTRATION NUMBER:

41/5.4.1/0781

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

Teva Pharmaceuticals (Pty) Ltd.

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