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Azilect® Media Backgrounder

ABOUT AZILECT®

What is Azilect®?

Azilect® (rasagiline 1mg) is a potent, second generation, highly selective, irreversible inhibitor of the enzyme monoamine oxidase-B (MAO-B)¹ which increases the availability of natural (endogenous) dopamine levels in patients with early Parkinson's disease (PD) and ensures that levodopa derived dopamine levels are optimised in moderate to advanced PD patients.

How does Azilect® work?

Azilect® works by inhibiting MAO-B, an enzyme that breaks down dopamine in the central nervous system.² Dopamine levels are therefore maintained when MAO-B is inhibited. Since dopamine plays a key role in regulating movement its depletion results in the emergence of the characteristic symptoms of PD: tremor, slowness of movement (bradykinesia), rigidity and postural instability.

How is Azilect® administered?

Azilect® is taken orally. It has a simple dosing regimen of one tablet taken once daily at any time, with or without food. Azilect® does not require titration, when taken either as monotherapy or as adjunctive therapy with other medications.² This means that Azilect® is a convenient and simple treatment for monotherapy and adjunct therapy in PD.²

Is Azilect® well tolerated?

Azilect® has been proven to be safe and well tolerated in both monotherapy and adjunct therapy in PD patients of all ages.^{3,4,5} In addition, long-term treatment with Azilect® has shown it to be efficacious, safe and well tolerated in PD patients.⁶

Does Azilect® have any side effects?

The most common side effects with Azilect® treatment are: headache, arthralgia (aching joints), dyspepsia, flu syndrome, depression, and minor



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gastro-intestinal problems.^{2,4} The frequency of dopaminergic adverse events in advanced PD is similar between patients treated with Azilect[®] and those treated with placebo (untreated).⁵ Azilect[®] does not cause significant cognitive or behavioural adverse events or adverse changes in mentation, behaviour or mood.² It is associated with a low discontinuation rate due to adverse events (4.2% with Azilect[®] vs 4.9% with placebo).

Who can benefit from Azilect[®]?

Azilect[®] is of benefit to early PD patients as monotherapy and to moderate and advanced PD patients as adjunctive therapy.² Studies have also shown that Azilect[®] benefits both younger and older patients.⁷

Azilect[®] is safe and well tolerated regardless of age, and has a low incidence of side effects, including those that are commonly seen with some dopaminergic therapies.⁸

Patients benefit from Azilect[®] because it is an efficacious, simple, well-tolerated and convenient treatment that is administered once daily and requires no titration.⁹

Can Azilect[®] improve quality of life?

Azilect[®] has been shown to improve health-related quality of life (HRQoL). It was the first PD therapy to demonstrate quality of life benefits in early PD patients¹⁰ and a recent review of studies of medical and surgical interventions in PD that used HRQoL as an outcome measure found that Azilect[®] was the only pharmacological treatment for PD to demonstrate efficacy in this parameter.¹¹

AZILECT[®]S BENEFITS IN EARLY PD

The therapeutic efficacy of oral, once-daily Azilect[®] as initial monotherapy in patients with early PD has been evaluated in the TEMPO trial. This randomised, double-blind, placebo-controlled trial was designed to study the efficacy of Azilect[®] over a 6 month period. TEMPO also assessed the effects of early vs. 6 months delayed start Azilect[®] monotherapy after 12 months of treatment and continued in an open label form for 6.5 years.



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Azilect® has shown significant improvements in the cardinal PD symptoms of tremor and bradykinesia (slowness of movement) among patients with early PD.³ Moreover, in the early vs. delayed start study, patients who started Azilect® earlier benefited from this advantage, suggesting that early use of Azilect® may both delay symptom progression and have the potential to delay disease progression.¹² The dual benefits of Azilect® - improvement in the symptoms of PD combined with a disease-modifying effect - have been confirmed by the results of the ADAGIO study.¹³

The TEMPO Study [TVP-1012 in Early Monotherapy for Parkinson's disease Outpatients]

- The initial 26-week double-blind, randomised placebo-controlled phase investigated the effect of Azilect® 1mg and 2mg vs. placebo in 404 patients with early PD.³
- The effect of Azilect® treatment was measured using the total Unified Parkinson's Disease Rating Scale (UPDRS), a diagnostic scale commonly used to measure a patient's ability to perform mental and motor tasks and activities of daily living.³
- Results from the initial 26-week phase of the study demonstrated that rasagiline is an effective therapy for patients with early PD.³
- In the second phase of the study, patients in the placebo group were switched to Azilect® 2mg at the end of 26 weeks of treatment, in order to measure the effect of delayed treatment start during additional 26 weeks of active treatment.¹²
- The primary outcome measure was the change in total UPDRS score between baseline and weeks 26 and 52 of treatment: secondary measures included Activities of Daily Living (ADL), motor function and quality of life scores measured on PD-QUALIF.¹²
- Results demonstrated that rasagiline monotherapy is an effective treatment for patients with early PD.³



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- **Key findings from TEMPO – 6 month results**

- Azilect® improved the total Unified Parkinson’s Disease Rating Scale (UPDRS), UPDRS-Motor and activities of daily living (ADL) subscale scores, compared to placebo.³
- Effect was also seen on secondary and exploratory endpoints, including cardinal PD signs (tremor, bradykinesia).³
- In patients with greater PD severity at baseline, Azilect® produced improvements versus placebo of >6 UPDRS units.³
- Adverse events were no more frequent in the group treated with Azilect® than those treated with placebo.³

- **Key findings from TEMPO – long-term results**

- Azilect® early start significantly delays decline in mean total UPDRS score over 12 months.^{3,6}
- At two years, 46% of patients remaining in the study were adequately controlled by Azilect® treatment only.⁶ Being able to control PD patients with one treatment reduces the need to add additional treatments such as L-dopa which can increase the risk of adverse side effects.¹⁴
- The benefit of early Azilect® treatment compared to delayed start of Azilect® was maintained over a period of 6.5 years, indicating that Azilect® may have disease modifying potential.⁶

Azilect®’s Key Benefits in Early PD

- Azilect® has been shown to be an effective and well tolerated 1st line treatment for patients with early signs of PD.³
- Early versus delayed treatment with Azilect® is associated with less PD symptom progression persisting over more than six years, suggesting a disease modifying potential.¹²
- After two years on treatment, approximately half of the patients remaining in the study were adequately maintained on Azilect® without any additional dopaminergic therapy.⁶



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The ADAGIO [Attenuation of Disease progression with Azilect® Given Once-daily] Study

- The ADAGIO trial is one of the largest studies in PD patients to specifically and prospectively investigate delaying disease progression. ADAGIO is a multi-centre, double-blind, placebo-controlled, parallel-group, delayed-start study. Study enrolment started in November 2005 and enrolment and randomisation were completed in just over one year with 1176 patients entering the trial.¹⁵
- With a mean disease duration of 5.4 (SD 4.6) months and baseline UPDRS-Total score of 20.4 (SD 8.5), this is one of the earliest PD populations ever to be studied in a randomised controlled trial.¹⁵ As a comparison, in the TEMPO trial, mean disease duration was 1.0 (SD 1.2) year, and mean baseline UPDRS score was 25.0 (SD 10.8).³

The first results from the ADAGIO trial are presented at the 2008 Congress of the EFNS. They confirm Azilect®'s dual benefits: improvement of the symptoms of PD combined with a disease-modifying effect.¹³

AZILECT®'S BENEFITS IN MODERATE TO ADVANCED PD

Most patients with moderate to advanced PD require a combination of drugs. Azilect® provides significant additional therapeutic benefits to patients who are already treated with levodopa or other PD medications, including dopamine agonists and entacapone.^{4,5}

Azilect®'s efficacy in moderate to advanced PD was studied in two multi-centre, randomised, placebo-controlled clinical trials, PRESTO and LARGO. Both studies showed that Azilect® is an effective once-daily adjunct therapy in moderate to advanced PD, which is safe and well tolerated even when used in addition to other PD therapies. In addition, Azilect® was shown to be a simple, convenient, once-daily treatment option.^{4,5}



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The primary outcome measure for both of these trials was the change from baseline in total daily "OFF" time, which corresponds to periods when the effects of PD medication have worn off and PD symptoms are no longer adequately controlled, causing motor fluctuations.^{4,5} Reducing "OFF" time and increasing "ON" time, without increasing the burden of medication side effects, are amongst the most significant clinical challenges in moderate to advanced PD.⁹ Both studies demonstrated that Azilect[®] 1mg is effective in reducing "OFF" time and improving motor fluctuations in moderate to advanced patients already optimised on other PD therapies.^{4,5}

The PRESTO Study⁴

- PRESTO investigated Azilect[®] 1mg and 0.5mg in a 26-week, double-blind, randomised, placebo-controlled study of 472 patients with moderate to advanced PD.
- Patients included in the study were already optimised on other PD medication, and had a mean of about 6 hours of daily "OFF" time.
- The primary outcome measure was the change in total daily "OFF" time, measured by patients' home diaries during 26 weeks of treatment.

The LARGO Study⁵

- The LARGO study, which included an active comparator arm, investigated Azilect[®] 1mg, entacapone (200mg with every levodopa dose) and placebo in an 18-week, double-blind, randomised trial of 687 patients with moderate to advanced PD.
- The primary outcome measure was the change in total daily "OFF" time.
- **Key findings from PRESTO and LARGO**
 - Azilect[®] significantly decreases "OFF" time and increases "ON" time.^{4,5}



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- Azilect® significantly increases total daily "ON" time without troublesome dyskinesia.^{4,5}
- Azilect® produces significant improvement vs. placebo on clinical global impression, and UPDRS ADL efficacy measures.^{4,5}
- Azilect® 1mg can deliver similar changes in "ON" and "OFF" time to multiple doses of entacapone 200mg.⁴
- Azilect® 1mg provides benefits to patients in the early morning, practically-defined "OFF" period (i.e. before the first drug dose). This benefit is linked to Azilect®'s 24-hour sustained efficacy, achieved through irreversible blocking of dopamine breakdown in the brain. A similar outcome was not seen with entacapone 200mg which has a short elimination half-life and duration of effect.⁵

Azilect®'s Key Benefits in Moderate to Advanced PD

- Azilect® is an effective once-daily adjunct therapy in moderate to advanced PD.^{4,5}
- Azilect®'s effect is of similar magnitude to that of entacapone in reducing "OFF" time.^{4,5}
- Azilect® significantly reduces the cardinal motor symptoms – tremor, rigidity, and bradykinesia.^{4,5}
- Azilect® offers additional therapeutic benefits in patients already taking other PD therapies.^{4,5}
- Azilect® is safe and well tolerated even when used in addition to other PD therapies.^{4,5}
- Azilect® is a simple, convenient, 1-tablet, once-daily treatment option.²

WHO MARKETS AZILECT®?

Azilect® is marketed in Europe by Lundbeck and Teva as part of a long-term strategic alliance between the two companies.

H. Lundbeck A/S is an international pharmaceutical company engaged in the research and development, production, marketing and sale of drugs



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for the treatment of psychiatric and neurological disorders. In 2006, the company's revenue was DKK 9.2 billion (approx. EUR 1.2 billion). The number of employees is approx. 5,000. For further information, visit www.lundbeck.com.

Teva Pharmaceutical Industries Ltd. (NASDAQ: TEVA), headquartered in Israel, is among the top 20 pharmaceutical companies and among the largest generic pharmaceutical companies in the world. The company develops, manufactures, and markets generic and innovative human pharmaceuticals and active pharmaceutical ingredients. Close to 90 percent of Teva's sales are in North America and Europe. Teva's innovative R&D focuses on developing novel drugs for diseases of the central nervous system.

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