SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SUNOSI® 75 mg
SUNOSI® 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sunosi® 75 mg
Each tablet contains 89.25 mg solriamfetol hydrochloride equivalent to 75 mg of solriamfetol.

Sunosi® 150 mg
Each tablet contains 178.50 mg solriamfetol hydrochloride, equivalent to 150 mg of solriamfetol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Sunosi® 75 mg film-coated tablets
Yellow to dark yellow/orange oblong tablet, approximately 7.6 mm x 4.4 mm, with "75" debossed on one side and a score line on the opposite side.
The tablet can be divided into equal doses.

Sunosi® 150 mg film-coated tablets
Yellow oblong tablet, approximately 9.5 mm x 5.6 mm, with "150" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sunosi is indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy (with or without cataplexy).

Sunosi is indicated to improve wakefulness and reduce excessive daytime sleepiness (EDS) in adult patients with obstructive sleep apnoea (OSA) whose EDS has not been satisfactorily treated by primary OSA therapy, such as continuous positive airway pressure (CPAP).

4.2 Posology and method of administration

Treatment should be initiated by a healthcare professional experienced in the treatment of narcolepsy or OSA.

Sunosi is not a therapy for the underlying airway obstruction in patients with OSA. Primary OSA therapy should be maintained in these patients.

Blood pressure and heart rate should be assessed before initiating treatment with solriamfetol and should be monitored periodically during treatment, especially after increasing the dose. Pre-existing hypertension should be controlled before initiating treatment with solriamfetol and caution should be exercised in treating patients at higher risk of major adverse cardiac events (MACE), particularly patients with pre-existing hypertension, patients with known cardiovascular or cerebrovascular disease and elderly patients.

The need for continued treatment with solriamfetol should be periodically assessed. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of solriamfetol or other appropriate medical intervention, discontinuation of solriamfetol should be considered. Caution should be exercised when using other medicinal products that increase blood pressure and heart rate (see section 4.5).

Posology

Narcolepsy
The recommended starting dose is 75 mg once daily, upon awakening. If clinically indicated in patients with more severe levels of sleepiness, a starting dose of 150 mg may be considered. Depending on clinical response, the dose can be titrated to a higher level by doubling the dose at intervals of at least 3 days, with a recommended maximum daily dose of 150 mg once daily.

OSA
The recommended starting dose is 37.5 mg once daily, upon awakening. Depending on clinical response, the dose can be titrated to a higher level by doubling the dose at intervals of at least 3 days, with a recommended maximum daily dose of 150 mg once daily.

Taking Sunosi less than 9 hours before bedtime should be avoided as it may affect night time sleep.

Long-term use
The need for continued treatment and the appropriate dose should be periodically assessed during extended treatment in patients prescribed solriamfetol.

Special populations

Elderly (> 65 years)
Limited data are available in elderly patients. Consideration should be given to the use of lower doses and close monitoring in this population (see section 4.4). Solriamfetol is predominantly eliminated by the kidney and since elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on creatinine clearance in these patients.

Renal impairment
Mild renal impairment (creatinine clearance of 60-89 mL/min): No dose adjustment is required.

Moderate renal impairment (creatinine clearance of 30-59 mL/min): The recommended starting dose is 37.5 mg once daily. Dose may be increased to a maximum of 75 mg once daily after 5 days.

Severe renal impairment (creatinine clearance of 15-29 mL/min): The recommended dose is 37.5 mg once daily.

End stage renal disease (creatinine clearance <15 mL/min): Solriamfetol is not recommended for use in patients with end stage renal disease.

Paediatric population
The safety and efficacy of Sunosi in children and adolescents (<18 years old) have not yet been established. No data are available.

Method of administration

Sunosi is for oral use.

Sunosi can be taken with or without food.

Administration of a 37.5 mg dose can be achieved by halving a 75 mg tablet using the score line.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias and other serious heart problems.
• Concomitant use of monoamine oxidase inhibitors (MAOI) or within 14 days after MAOI treatment has been discontinued (see section 4.5).

4.4 Special warnings and precautions for use

Psychiatric symptoms

Solriamfetol has not been evaluated in patients with a history of or concurrent psychosis or bipolar disorders. Caution should be exercised when treating these patients due to psychiatric adverse reactions that could exacerbate symptoms (e.g. manic episodes) of pre-existing psychiatric disorders.

Patients treated with solriamfetol should be carefully monitored for adverse reactions such as anxiety, insomnia and irritability. These adverse reactions were commonly observed during treatment initiation, but tended to resolve with continued treatment. If these symptoms persist or worsen, dose reduction or discontinuation should be considered.

Blood pressure and heart rate

Analyses of data from clinical trials showed that treatment with solriamfetol increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose dependent fashion.

Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular event (MACE), including stroke, heart attack and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for

MACE, including hypertension, diabetes, hyperlipidemia and high body mass index (BMI).

Use in patients with unstable cardiovascular disease, serious heart arrhythmias and other serious heart problems is contraindicated (see section 4.3).

Patients with moderate or severe renal impairment may be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of solriamfetol.

Abuse

Sunosi was assessed in a human abuse potential study and demonstrated low abuse potential. Results from this clinical study demonstrated that solriamfetol produced Drug Liking scores higher than placebo, but generally similar or lower than phentermine (a weak stimulant). Caution should be exercised when treating patients with a history of stimulant (e.g. methylphenidate, amphetamine) or alcohol abuse, and these patients should be monitored for signs of misuse or abuse of solriamfetol.

Angle closure glaucoma

Mydriasis may occur in patients taking solriamfetol. Caution is advised in patients with increased ocular pressure or at risk of angle closure glaucoma.

Women of childbearing potential or their partners

Women of childbearing potential or their male partners must use effective method of contraception while taking solriamfetol (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed (see section 5.2).

Solriamfetol must not be administered concomitantly with MAOIs or within 14 days after MAOI treatment has been discontinued because it may increase the risk of a hypertensive reaction (see section 4.3).

Concomitant use of medicinal products that increase blood pressure and heart rate should be used with caution (see section 4.4).

Medicinal products that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with solriamfetol. Concomitant use of such medicinal products should be used with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of solriamfetol in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Sunosi is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

Solriamfetol is excreted in human milk at approximately 4 % of the maternal dose on a weight-adjusted basis (see section 5.2). The effect of solriamfetol on newborns/infants or its impacts on milk production are unknown. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Sunosi therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the women.
Infants exposed to solriamfetol should be monitored for signs of agitation, insomnia, and reduced weight gain.

Fertility

The effects of solriamfetol in humans are unknown. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Minor influence on the ability to drive is expected in patients receiving stable solriamfetol doses. Dizziness and disturbance in attention may occur following administration of solriamfetol (see section 4.8).

Patients with abnormal levels of sleepiness who take solriamfetol should be advised that their level of wakefulness may not return to normal. Patients with excessive daytime sleepiness, including those taking solriamfetol should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity, especially at the start of the treatment or when the dose is changed.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were headache (11.1%), nausea (6.6%) and decreased appetite (6.8%).

Tabulated list of adverse reactions

The frequency of adverse reactions is defined using the following MedDRA frequency convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Adverse reactions**	**Frequency**
Metabolism and nutrition disorders	Decreased appetite	Common
Psychiatric disorders	Anxiety	Common
	Insomnia	Common
	Irritability	Common
	Bruxism	Common
	Agitation	Uncommon
	Restlessness	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness	Common

	Disturbance in attention	Uncommon
	Tremor	Uncommon
Cardiac disorders	Palpitations	Common
	Tachycardia	Uncommon
Vascular Disorders	Hypertension	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Dyspnoea	Uncommon
Gastrointestinal disorders	Nausea	Common
	Diarrhoea	Common
	Dry mouth	Common
	Abdominal pain	Common
	Constipation	Common
	Vomiting	Common
Skin and subcutaneous tissue disorders	Hyperhidrosis	Common
General disorders and administration site conditions	Feeling jittery	Common
	Chest discomfort	Common
	Chest pain	Uncommon
	Thirst	Uncommon
Investigations	Heart rate increased	Uncommon
	Blood pressure increased	Common
	Weight decreased	Uncommon

Description of selected adverse reactions

Treatment initiation
The majority of the most frequently reported adverse reactions occurred within the first 2 weeks of initiating treatment and resolved for the majority of patients with a median duration of less than 2 weeks.

Hypersensitivity reactions
In post-marketing experience, there have been reports of hypersensitivity reactions which have occurred with one or more of the following: rash erythematous, rash, urticaria (see section 4.3).

Dose-dependent adverse reactions
In the 12-week clinical trials that compared doses of 37.5 mg, 75 mg and 150 mg/day of solriamfetol to placebo, the following adverse reactions were dose-related: headache, nausea, decreased appetite, anxiety, diarrhoea and dry mouth. The dose relationships were generally similar in OSA and narcolepsy patients. Certain events such as anxiety, insomnia, irritability, and agitation were commonly observed during treatment initiation but tended to resolve with continued treatment. If these symptoms persist or worsen, dose reduction or discontinuation should be considered (see section 4.4).

Discontinuation of treatment
In the 12-week placebo-controlled clinical trials, 11 of the 396 patients (3%) who received solriamfetol discontinued due to an adverse reaction compared to 1 of the 226 patients (<1%) who received placebo. The adverse reactions leading to discontinuation that occurred in more than one solriamfetol-treated patients and at a higher rate than placebo were anxiety, palpitations and restlessness, all of which occurred with a frequency less than 1%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

There have been no reports of overdose of solriamfetol in the clinical studies.

In healthy volunteers, there was one adverse reaction of mild tardive dyskinesia and one adverse reaction of moderate akathisia that occurred at a supratherapeutic dose of 900 mg; symptoms resolved after treatment discontinuation.

There is no specific antidote. In the case of inadvertent overdose, symptomatic and supportive medical care should be provided and patients should be carefully monitored, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, centrally acting sympathomimetics, ATC code: N06BA14

Mechanism of action

The mechanism(s) of solriamfetol to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea has not been fully characterised. However, its efficacy could be mediated through its activity as a dopamine and norepinephrine reuptake inhibitor (DNRI).

Pharmacodynamic effects

In vitro data
In radioligand-binding experiments with cells expressing cloned human receptors/transporters, solriamfetol showed affinity for the dopamine (replicate Ki=6.3 and 14.2 µM) and norepinephrine transporter (replicate Ki= 3.7 and >10 µM) but no appreciable affinity to the serotonin transporter. Solriamfetol inhibited the reuptake of dopamine (replicate IC_{50}=2.9 and 6.4 µM) and norepinephrine (IC_{50}= 4.4 µM) but not of serotonin by these cells.

In vivo animal data
In parenteral doses resulting in clear wake-promoting effects in rats, solriamfetol increased individual dopamine levels in the striatum and norepinephrine levels in the prefrontal cortex, and did not show appreciable binding to the rat dopamine and norepinephrine transporter in an autoradiography experiment.

Clinical efficacy and safety

Narcolepsy

Study 1, a 12-week, randomised, double-blind, placebo-controlled, parallel-group study, evaluated the efficacy of solriamfetol in adult patients with narcolepsy (with or without cataplexy).

For entry into this study patients had to have excessive daytime sleepiness (an Epworth Sleepiness Scale [ESS] score greater than or equal to 10), and trouble maintaining wakefulness (mean sleep latency less than 25 minutes) as documented by the mean of the first 4 trials of the 40-minute Maintenance of Wakefulness Test (MWT) at baseline.

The measures of efficacy were change from baseline to Week 12 on: ability to stay awake as measured by mean sleep latency on the MWT, excessive daytime sleepiness as measured by the ESS, and improvement in overall clinical condition as assessed by the Patient Global Impression of Change (PGIc) scale. The ESS is an 8-item patient-reported measure of likelihood of falling asleep in usual daily life activities. The PGIc is a 7-point scale ranging from “very much improved” to “very much worse” which assesses the patient’s report of change in their clinical condition.

Patients with narcolepsy were characterised by impaired wakefulness and excessive daytime sleepiness, as indicated by baseline MWT mean sleep latency and ESS scores, respectively (Table 1). Most patients had prior use of psychostimulants. Cataplexy was present in approximately half of patients overall; demographic and baseline characteristics were similar between patients with cataplexy and those without cataplexy.

In this study, patients with narcolepsy were randomised to receive solriamfetol 75 mg, 150 mg, or 300 mg (two times the maximum recommended daily dose), or placebo once daily. At Week 12, patients randomised to the 150 mg dose showed statistically significant improvements on the MWT and ESS (co-primary endpoints), as well as on the PGIc (key secondary endpoint), compared with placebo. Patients randomised to receive 75 mg showed statistically significant improvement on the ESS, but not on the MWT or PGIc (Table 1). These effects were dose-dependent, observed at Week 1 and maintained over the study duration (Figure 1). In general, at the same doses, a smaller magnitude of effect was observed in patients with more severe baseline levels of sleepiness relative to those who were less severe. At Week 12, patients who were randomised to receive 150 mg of solriamfetol demonstrated sustained improvements in wakefulness throughout the day that were statistically significant compared to placebo for each of the 5 MWT trials, spanning approximately 9 hours after dosing. Dose-dependent improvements in the ability to conduct daily activities were observed, as measured by the Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10). Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Night-time sleep as measured with polysomnography was not affected by the use of solriamfetol.

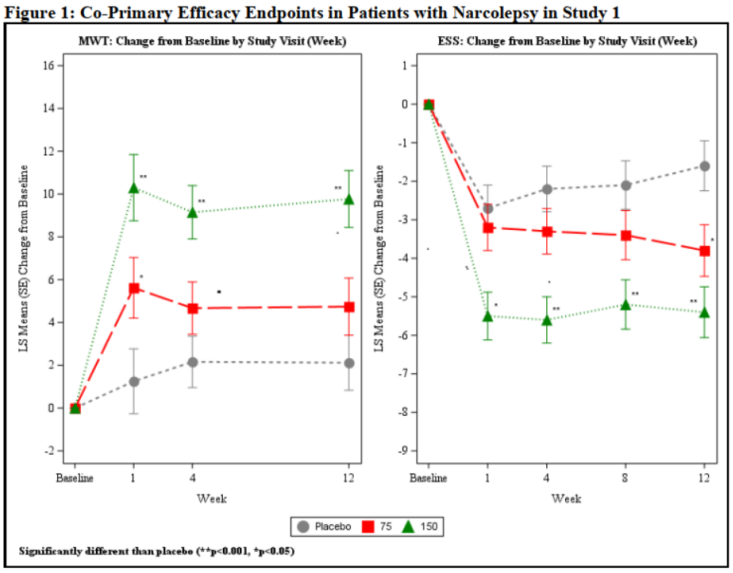
Table 1. Overview of Efficacy Results at Week 12 in Patients with Narcolepsy in Study 1

	Treatment Groups (N)	Mean Baseline Score (SD)	Mean Change from Baseline	Difference from Placebo (95% CI)	P - Value

MWT (min)	*Study 1* Placebo (58) Sunosi 75 mg (59) Sunosi 150 mg (55)	6.15 (5.68) 7.50 (5.39) 7.85 (5.74)	**LS Mean (SE)** 2.12 (1.29) 4.74 (1.34) 9.77 (1.33)	2.62 (-1.04, 6.28) 7.65 (3.99, 11.31)	0.1595 <0.0001
	Study 1 Placebo (58) Sunosi 75 mg (59) Sunosi 150 mg (55)	17.3 (2.86) 17.3 (3.53) 17.0 (3.55)	**LS Mean (SE)** -1.6 (0.65) -3.8 (0.67) -5.4 (0.66)	-2.2 (-4.0, -0.3) -3.8 (-5.6, -2.0)	0.0211 <0.0001
		Percentage of Patients Improved*		**Percentage Difference from Placebo (95% CI)**	**P - Value**
PGIc	*Study 1* Placebo (58) Sunosi 75 mg (59) Sunosi 150 mg (55)	39.7% 67.8% 78.2%		28.1 (10.8, 45.5) 38.5 (21.9, 55.2)	0.0023† <0.0001

SD = Standard Deviation; SE = Standard Error; LS Mean = Least Square Mean; Difference From Placebo = LS Mean Difference between change from baseline between active drug and placebo. MWT results are derived from the first 4 trials of the MWT and a positive change from baseline represents improvement in the sleep latency time. On the ESS, a negative change from baseline represents improvement in excessive daytime sleepiness. *The percentage of patients improved on the PGIc includes those who reported very much, much and minimal improvements; †Nominal p-value.

Figure 1: Co-Primary Efficacy Endpoints in Patients with Narcolepsy in Study 1



OSA

Study 2, a 12-week, randomised, double blind, placebo-controlled parallel-group study, evaluated the efficacy of solriamfetol in adult patients with OSA. The co-primary and key secondary endpoints in this study were identical to Study 1. Study 3 was a 6-week, randomised-withdrawal, double-blind, placebo-controlled study of the efficacy of solriamfetol in adult patients with OSA. The measures of efficacy in the randomised withdrawal period were change from the beginning to the end of the randomised-withdrawal period on the MWT, the ESS, and worsening in overall clinical condition as assessed by the PGIc.

For entry into both studies, patients had to have excessive daytime sleepiness (ESS score ≥10) and trouble maintaining wakefulness (mean sleep latency <30 minutes as documented by the mean of the first 4 trials of the MWT) at baseline. Patients were eligible if they: 1) were currently using a primary OSA therapy (at any level of adherence); 2) had previously used a primary therapy for at least one month with at least one documented adjustment to the therapy; or 3) had undergone a surgical intervention in an attempt to treat the underlying obstruction. Patients were encouraged to stay on their current primary OSA therapy at the same level of use throughout the study. Patients were excluded only on the basis of their primary therapy use if they had refused to try a primary therapy such as CPAP, an oral appliance, or a surgical intervention to treat their underlying obstruction.

In Study 2, patients with OSA were characterised by impaired wakefulness and excessive daytime sleepiness (EDS), as indicated by baseline MWT mean sleep latency and ESS scores, respectively (Table 2). Approximately 71% of patients were adherent (e.g. ≥4 hours per night on ≥70% of nights); demographic and baseline characteristics were similar between patients regardless of adherence to primary OSA therapy. At baseline, primary OSA therapy was used by approximately 73% of patients; of these patients, 92% of patients were using positive airway pressure (PAP).

Patients were randomised to receive solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg (two times the maximum recommended daily dose), or placebo once daily. At Week 12, patients randomised to the 75 mg and150 mg dose arms showed statistically significant improvements on the MWT and ESS (co-primary endpoints), as well as on the PGIc (key secondary endpoint), compared with placebo (Table 2). Patients randomised to 37.5 mg solriamfetol showed statistically significant improvements based on the MWT and ESS. These effects were observed at Week 1, maintained over the study duration and were dose-dependent (Figure 2). At Week 12, patients who were randomised to receive 75 mg and 150 mg of Sunosi demonstrated sustained improvements in wakefulness throughout the day that were statistically significant compared to placebo for each of the 5 MWT trials, spanning approximately 9 hours after dosing. Dose- dependent improvements in the ability to conduct daily activities were observed, as measured by the FOSQ-10. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Night-time sleep as measured with polysomnography was not affected by the use of solriamfetol in Study 2. No clinically meaningful changes in patient use of primary OSA therapy were observed across the 12-week study period in any treatment group. Adherence/non-adherence to primary OSA therapy did not suggest evidence of differential efficacy.

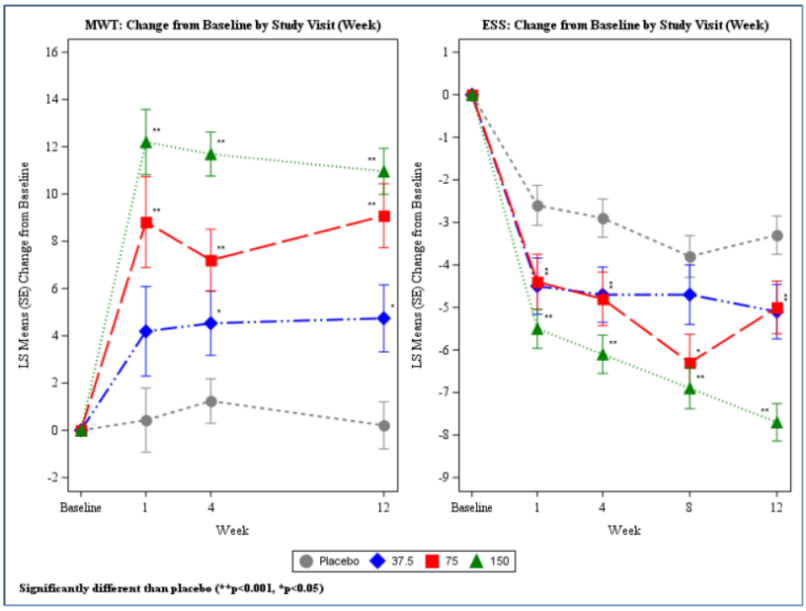
In Study 3, baseline demographics and disease characteristics were similar to the study population in Study 2. The dose was initiated at 75 mg once daily and could be titrated up one dose level in intervals no shorter than every 3 days, according to efficacy and tolerability, to 150 mg or 300 mg. Patients could also titrate down to 75 mg or 150 mg. Patients treated with solriamfetol remained improved, whereas placebo-treated patients worsened (LS mean difference of 11.2 minutes on MWT and -4.6 on ESS; both $p<0.0001$) during the randomised-withdrawal period after 4 weeks of open-label treatment. Fewer patients treated with solriamfetol reported worsening on the PGIc (percentage difference of 30%; $p=0.0005$).

Table 2. Overview of Efficacy Results at Week 12 in Patients with OSA in Study 2

	Treatment Group (N)	Mean Baseline Score (SD)	Mean Change from Baseline	Difference from Placebo (95% CI)	P -Value
MWT (min)	Placebo (114) Sunosi 37.5 mg (56) Sunosi 75 mg (58) Sunosi 150 mg (116)	 12.58 (7.14) 13.6 (8.15) 12.44 (6.91) 12.54 (7.18)	**LS Mean (SE)** 0.21 (1.0) 4.74 (1.42) 9.08 (1.36) 10.96 (0.97)	- 4.53 (1.16, 7.90) 8.87 (5.59, 12.14) 10.74 (8.05, 13.44)	- 0.0086 <0.0001 <0.0001
ESS	Placebo (114) Sunosi 37.5 mg (56) Sunosi 75 mg (58) Sunosi 150 mg (116)	 15.6 (3.32) 15.1 (3.53) 15.0 (3.51) 15.1 (3.37)	**LS Mean (SE)** -3.3 (0.45) -5.1 (0.64) -5.0 (0.62) -7.7 (0.44)	- -1.9 (-3.4, -0.3) -1.7 (-3.2, -0.2) -4.5 (-5.7, -3.2)	- 0.0161 0.0233 <0.0001
		Percentage of Patients Improved*		**Percentage Difference from Placebo (95% CI)**	**P -Value**
PGIc	Placebo (114) Sunosi 37.5 mg (56) Sunosi 75 mg (58) Sunosi 150 mg (116)	49.1% 55.4% 72.4% 89.7%		- 6.2 (-9.69, 22.16) 23.3 (8.58, 38.01) 40.5 (29.81, 51.25)	- 0.4447 0.0035 <0.0001

SD = Standard Deviation; SE = Standard Error; LS Mean = Least Square Mean; Difference From Placebo = LS Mean Difference on change from baseline between active drug and placebo. MWT results are derived from the first 4 trials of the MWT and a positive change from baseline represents improvement in the sleep latency time. On the ESS, a negative change from baseline represents improvement in excessive daytime sleepiness. *The percentage of patients improved on the PGIc includes those who reported very much, much and minimal improvements.

Figure 2: Co-Primary Efficacy Endpoints in Patients with OSA in Study 2



Long-term efficacy in narcolepsy and OSA
Study 4 was a long-term safety and maintenance of efficacy study for up to a year of treatment with solriamfetol, including a 2-week randomised-withdrawal, placebo-controlled period after at least 6 months of treatment with solriamfetol, in adult patients with narcolepsy or OSA who had completed a prior trial.

The measures of efficacy in the randomised withdrawal period were change from the beginning to the end of the randomised-withdrawal period on the ESS and worsening in overall clinical condition as assessed by the PGIc. Dose initiation and titration was identical to Study 3.

Patients treated with solriamfetol remained improved, whereas placebo-treated patients worsened (LS mean difference of -3.7 on ESS; $p<0.0001$) during the randomised-withdrawal period after at least 6 months of open-label treatment. Fewer patients treated with solriamfetol reported worsening on the PGIc (percentage difference of -36.2%; $p<0.0001$). These results demonstrate long-term maintenance of efficacy with continued solriamfetol treatment, and a reversal of treatment benefit upon discontinuation of that treatment.

For patients who were using a primary OSA therapy at the beginning of the study, primary OSA therapy use did not change over the course of the long-term study.

5.2 Pharmacokinetic properties

Absorption

The oral bioavailability of solriamfetol is approximately 95% with peak plasma concentrations occurring at a median T_{max} of 2 hours (range 1.25 to 3 hours) under fasted conditions.

Ingestion of solriamfetol with a high-fat meal resulted in minimal changes in C_{max} and AUC; however, a delay of approximately 1 hour was observed in T_{max}. The results show that solriamfetol can be taken without regard to food.

Distribution

The apparent volume of distribution of solriamfetol is approximately 198.7 L, indicating extensive tissue distribution beyond the vascular compartment. Plasma protein binding ranged from 13.3% to 19.4% over the solriamfetol concentration range of 0.059 to 10.1 µg/mL in human plasma. The mean blood-to-plasma concentration ratio ranged from 1.16 to 1.29, suggesting a small extent of binding of solriamfetol to blood cells.

Biotransformation

Solriamfetol is minimally metabolised in humans.

Interactions
With the exception of weak inhibition of CYP2D6 (IC_{50} of 360 µM), solriamfetol is not a substrate or inhibitor of any of the major CYP enzymes and does not induce CYP1A2, 2B6, 3A4 or UGT1A1 enzymes at clinically relevant concentrations. Solriamfetol does not appear to be a substrate or inhibitor of membrane transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1 or OAT3. Solriamfetol is primarily excreted unchanged in the urine and is a low-affinity substrate of multiple renal

cationic active substance transporters, without strong affinity for any individual transporter tested (OCT2, MATE1, OCTN1 and OCTN2). Solriamfetol is not an inhibitor of renal transporters OCT1, MATE2K, OCTN1 or OCTN2 but is a weak inhibitor of OCT2 (IC_{50} of 146 µM) and MATE1 (IC_{50} of 211 µM). Taken together, these results show that clinically relevant PK drug interactions are unlikely to occur in patients taking solriamfetol.

Elimination

The apparent mean elimination half-life of solriamfetol is 7.1 hours, and the apparent total clearance is approximately 19.5 L/h. Renal clearance for solriamfetol is approximately 18.2 L/h.

In a human mass-balance study, approximately 95% of the dose was recovered in urine as unchanged solriamfetol and 1% or less of the dose was recovered as the minor inactive metabolite N-acetyl solriamfetol. Renal clearance represented the majority of apparent total clearance and exceeded creatinine clearance by approximately 3-fold, indicating that active tubular secretion of the parent drug is likely the major elimination pathway.

Linearity/non-linearity

Solriamfetol exhibits linear pharmacokinetics over the clinical dose range. Steady state is reached in 3 days, and once-daily administration of 150 mg is expected to result in minimal solriamfetol accumulation (1.06 times single-dose exposure).

Special populations

Renal impairment
Compared to subjects with normal renal function (eGFR≥90 mL/min/1.73 m_2), AUC of solriamfetol was higher by approximately 1.5-, 2.3-, and 4.4-fold, and $t_{1/2}$ increased approximately 1.2-, 1.9-, and 3.9- fold in patients with mild (eGFR 60-89 mL/min/1.73 m_2), moderate (eGFR 30-59 mL/min/1.73 m_2), or severe (eGFR<30 mL/min/1.73 m_2) renal impairment, respectively. In general, mean C_{max} and median T_{max} values were not affected by renal impairment.

Compared to subjects with normal renal function (eGFR≥90 mL/min/1.73 m_2), AUC of solriamfetol was higher by approximately 6.2- and 4.6-fold, respectively, in patients with ESRD without hemodialysis and in patients with ESRD undergoing hemodialysis, and $t_{1/2}$ increased at least 13-fold. Solriamfetol is not recommended for use in patients with ESRD. In patients with ESRD, an average of 21% of solriamfetol was removed by hemodialysis.

Lactation and Breast-feeding

A single-dose milk and plasma lactation study was conducted in 6 healthy adult lactating women who were between 15 and 37 weeks postpartum and were administered a single oral 150 mg dose of Sunosi. The cumulative mean amount excreted in breast milk was 0.59 mg over 24 hours, which is about 4% of the maternal dose on a weight-adjusted basis. Of the total amount of solriamfetol excreted in breast milk over 72 hours, approximately 78% and 98% were excreted by 8 and 24 hours, respectively, with an apparent mean elimination half-life in breast milk of about 5 hours.

Age, gender, race
Population PK analysis indicated that the intrinsic covariates of age, gender, and race do not have clinically relevant effects on the pharmacokinetics of solriamfetol.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity, and male and female fertility.

Repeated dose toxicity studies with daily oral application were conducted in mice (duration 3 months, NOAEL 17 mg/kg/day), rats (duration 6 months with a 3-month recovery period, NOAEL not established, LOAEL 29 mg/kg/day) and dogs (duration 12 months with a 3-month recovery period, NOAEL not established, LOAEL 8 mg/kg/day). AUC-based safety factors for solriamfetol derived from these studies (based on comparison with clinical AUC at the maximum recommended human dose of 150 mg/day) were <1 for mice (based on NOAEL) and <2 for rats and dogs (based on LOAEL), mainly due to exaggerated pharmacological effects of solriamfetol on CNS activity.

Long-term carcinogenicity studies have been performed in mice, treated with oral solriamfetol doses of 20, 65 and 200 mg/kg/day for up to 104 weeks, and in rats, treated with oral solriamfetol doses of 35, 80 and 200 mg/kg/day for up to 101 weeks. Solriamfetol did not increase the incidence of neoplastic findings in these lifetime carcinogenicity assays. AUC-based safety margins at the high dose to the maximal recommended human dose (MRHD, 150 mg/day) were about 7.8 in mice and about 20.7 in rats. In the light of negative genotoxicity and no increase of tumour incidence in both carcinogenicity studies, it can be concluded that solriamfetol does not pose a carcinogenic risk to humans. Compared to controls, survival rate was decreased in solriamfetol-treated (male) mice, maximal at a dose of 65 mg/kg/day (AUC-based safety margin to MRHD about 2.9), but not in solriamfetol-treated rats.

Embryofoetal development

Possible effects on embryofoetal development were investigated in pregnant rats and rabbits. Embryofoetal toxicity (increased postimplantation loss in rats, increased incidence of skeletal alterations that included sternebrae malalignment in rats and rabbits, hindlimb rotation and bent bones in rats, and decreased foetal weights in both species) and situs inversus in rats was only evident in the presence of maternal toxicity (decreased body weights). Whether embryotoxicity was a consequence of maternal toxicity or a direct effect of solriamfetol cannot be determined. In a distribution study in pregnant rats 14C-solriamfetol was detected in foetal membrane (around twice as high as in blood), placenta and whole foetus (nearly similar to blood concentration) and thus a direct toxic effect on the foetus cannot be excluded. In rats the exposure margins at the maternal and developmental NOAEL are below the human exposure (0.6 – 0.7 based on AUC) at the MRHD, while in rabbits the exposure margins at the maternal and developmental NOAEL is < 6 (based on mg/m^2 body surface area).

Prenatal and postnatal Development

In rats exposure levels (AUC) above 0.6 – 0.7 times the human exposure (AUC) at the MRHD during pregnancy and lactation resulted in maternal toxicity and adverse effects on growth and development in the offspring. At exposure levels (AUC) 8 to 12

times the human exposure (AUC) at the MRHD no long-term effects on learning and memory were observed, but mating and pregnancy indices of the offspring were decreased.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydroxypropyl cellulose (HPC)
Magnesium stearate (MgSt)

Film coating
Polyvinyl alcohol
Polyethylene glycol (Macrogol)
Titanium dioxide
Talc
Yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Bottles after first opening: use within 120 days.

6.4 Special precautions for storage

Blisters: Store below 25°C.

Bottles: Store below 25°C. Keep the container tightly closed in order to protect from moisture. Once opened, use within 120 days, store below 25°C.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister.
Packs containing 7, 28 or 56 film-coated tablets.

High density polyethylene (HDPE) bottle with polypropylene (PP) child-resistant cap with integrated silica gel desiccant. Each bottle contains 30 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

NEOPHARM Ltd.,

HaShiloach 6, POB 7063, Petach Tikva 4917001, Israel.

8. IMPORTER

NEOPHARM (ISRAEL) 1996 Ltd.,
HaShiloach 6, POB 7063, Petach Tikva 4917001, Israel.

9. MARKETING AUTHORISATION NUMBERS

Sunosi 75 mg: 172-80-37284-99
Sunosi 150 mg: 172-81-37285-99

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