Date: 1 June 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Sunosi

International non-proprietary name: solriamfetol
Pharmaceutical form: film-coated tablets
Dosage strength(s): 150 mg, 75 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Clinipace AG
Marketing Authorisation No.: 68177
Decision and Decision date: approved on 22 March 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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Table of contents

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CPAP	Continuous positive airway pressure
CYP	Cytochrome P450
DDI	Drug-drug interaction
EDS	Excessive daytime sleepiness
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
KF	Karl Fischer
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
OSA	Obstructive sleep apnoea
PBPK	Physiologically-based pharmacokinetic
PD	Pharmacodynamics
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSP	Pediatric Study Plan (US-FDA)
REM	Rapid eye movement
RMP	Risk Management Plan
RT	Retention time
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UV	Ultraviolet Spectrometry

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance solriamfetol of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Sunosi is indicated to improve wakefulness and reduce excessive daytime sleepiness in adult patients with narcolepsy or obstructive sleep apnoea (OSA).
Restrictions in administration
Sunosi is not indicated for the treatment of the underlying airway obstruction in patients suffering from obstructive sleep apnoea (OSA).

2.2.2 Approved Indication

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.
Sunosi is indicated to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy.

Limitations of use

Sunosi is not indicated for a causal treatment (primary therapy) of underlying airway obstruction in OSA. Prior to treatment of excessive daytime sleepiness with Sunosi, primary OSA therapy (e.g., CPAP) must have been instituted for an adequate duration or, at the very least, attempted. Primary OSA therapy is to be maintained during treatment with Sunosi. Sunosi is not a replacement for primary OSA therapy."

2.2.3 Requested Dosage

Sunosi can be taken with or without food. Taking Sunosi less than 9 hours before bedtime should be avoided as it may affect nighttime sleep.

Dosage

Narcolepsy
The recommended initial dose is 75 mg once daily in the morning after waking up. For patients showing more excessive sleepiness, an initial dose of 150 mg may be considered if clinically indicated.

Depending on clinical response, the dose can be titrated to a higher level by doubling the dose after an interval of at least 3 days, with a recommended maximum daily dose of 150 mg once daily.

OSA
The recommended initial dose is 37.5 mg once a day in the morning after waking up. Depending on the 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.

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Long-term use: The need for continued treatment and the appropriate dosage should be assessed regularly in patients receiving long-term treatment with Sunosi.

Patients with impaired renal function
Mild renal impairment (creatinine clearance 60-89 mL/min): No dosage adjustment is necessary.
Moderate renal impairment (creatinine clearance 30-59 mL/min): The recommended starting dose is 37.5 mg once daily. The dose may be increased after 5 days to a maximum of 75 mg once daily.
Severe renal impairment (creatinine clearance 15-29 mL/min): The recommended dose is 37.5 mg once daily.
End-stage renal disease (creatinine clearance <15 mL/min): Sunosi is not recommended for use in patients with end-stage renal disease.

Elderly patients (> 65 years)
Of all the patients treated with Sunosi in the clinical studies for narcolepsy and OSA, 13% (125/935) were aged 65 or older.
No clinically relevant differences in safety or efficacy were observed between younger and older people.

Solriamfetol is mainly eliminated by the kidneys. Because renal impairment is more common in the elderly, the dosage may need to be adjusted according to the patient's creatinine clearance.

Children and adolescents
The safety and efficacy of Sunosi in children and adolescents (<18 years) have not yet been established.

No clinical studies have investigated the administration in children and adolescents.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	1 September 2020
Formal control completed	22 October 2020
List of Questions (LoQ)	11 February 2021
Answers to LoQ	5 May 2021
Predecision	19 July 2021
Answers to Predecision	6 September 2021
Labelling corrections	30 November 2021
Answers to Labelling corrections	7 January 2022
Final Decision	22 March 2022
Decision	approval

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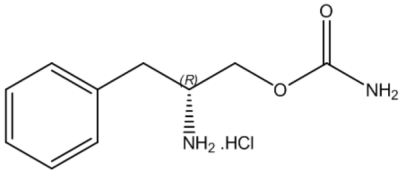
3 Medical Context

Narcolepsy is a chronic sleep disorder which affects the ability to regulate sleep-wake cycles EDS, typically associated with cataplexy (Narcolepsy I) and other rapid eye movement (REM) sleep conditions. The presence of EDS is a defining characteristic of narcolepsy and a major diagnostic criterion. The degree of EDS is severe in most patients. OSA is a serious disorder characterised by sleep fragmentation caused by repeated arousals secondary to partial or complete obstruction of the upper airway during sleep. Persistent EDS is a major presenting complaint in many patients, and most patients with OSA awaken in the morning feeling tired and unrefreshed regardless of the duration of their time in bed. As with narcolepsy, the persistent sleepiness in patients with OSA occurs at inappropriate times, for instance while actively conversing, eating, working, and driving (American Academy of Sleep Medicine [AASM] 2014). In the presented studies, both narcolepsy and OSA diagnosis were established according to the International Classification of Sleep Disorders 3rd ed. (ICSD-3). For narcolepsy, about every second narcoleptic patient included in the pivotal trial 14-002 presented with cataplectic events. The clinical development of solriamfetol follows a symptom-oriented approach, intended to improve wakefulness and reduce EDS. Sunosi film-coated tablets are proposed to improve wakefulness and reduce EDS in adult patients with narcolepsy (with or without cataplexy) or obstructive sleep apnoea (OSA).

4 Quality Aspects

4.1 Drug Substance

INN: solriamfetol
Chemical name: (R)-2-amino-3-phenylpropylcarbamate hydrochloride
Molecular formula: $C_{10}H_{14}N_2O_2.HCl$
Molecular mass: 194.23 g mol $^{-1}$ (free base); 230.69 g mol $^{-1}$ (as hydrochloride (HCl) salt)
Molecular structure:



Physico-chemical properties: solriamfetol is a white to off-white crystalline solid. It possesses one chiral centre at position 2. It is highly soluble in the biopharmaceutical classification system. It is hygroscopic above 75 % relative humidity.

Synthesis: solriamfetol is synthesised by a two-step chemical synthesis, salt formations and the final crystallisation. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Structure elucidation:
The structure of solriamfetol has been fully elucidated using several spectroscopic techniques such as mass spectrometry, infrared spectroscopy, nuclear magnetic resonance spectroscopy, X-ray crystallography and specific rotation.

Specification:
The active substance specification includes all tests as recommended by the relevant ICH guidelines.

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Stability: A stability study has been carried out according to the current guideline recommendations. Based on the results of this study, a satisfactory retest period was established.

4.2 Drug Product

Description and composition: solriamfetol drug product is a film-coated immediate-release tablet. Each strength tablet is differentiated by size, weight and a different shade of yellow and debossed on one side with “75” and “150” respectively. The 75 mg tablet has a score line on the opposite side to the debossed text. The excipients of the tablet cores are hydroxypropyl cellulose and magnesium stearate. The yellow film coating of the tablet is composed of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide (E171) and yellow iron oxide (E172).

Pharmaceutical development: Sunosi tablets were developed as immediate-release film-coated tablets.

Manufacture: The manufacturing process is described in sufficient detail. In order to achieve a consistent quality of the tablets, appropriate in-process controls are applied.

Specification: For the control of the finished product, adequate tests and criteria for release and at shelf life are established. The specifications include the parameters description (visual examination), identification (HPLC, UV and HPLC, RT), assay (HPLC), content uniformity by weight variation, degradation products (HPLC), water content (Karl Fischer) and dissolution testing. The test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container Closure System: The solriamfetol film-coated tablets are packaged in blisters.

Stability: Appropriate stability data are presented. Based on these data, a shelf life was established.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application of Sunosi (solriamfetol), Division Nonclinical Assessment, conducted an abridged evaluation, which was based on the European Medicines Agency (EMA) assessment report (EMA/686622/2019, dated 14 November 2019) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Sunosi in the proposed indication. The pharmaco-toxicological profile of solriamfetol has been sufficiently characterised in nonclinical species (mice, rats, and dogs). There were no safety issues identified in the nonclinical studies that would be of concern for human use. Many of the dose-limiting toxicities in animal studies were due to a pharmacology-related action on the central nervous system and/or body weight decrease, which are clinically monitorable and were reversible on treatment cessation. There are no safety margins between exposure in animals and humans. This is acceptable since no unacceptable risks for the proposed indication were identified.

Sunosi is not intended for use in a paediatric population. EMA/PDCO agreed on a PIP (EMEA-002184-PIP01-17) for solriamfetol. All nonclinical measures were completed, and no particular risks for the paediatric population were identified.

There is no safety concern regarding excipients and impurities.

Based on the ERA, the risk for the environment is low.

All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical pharmacology and clinical aspects of this application and relies on the assessment of the EMA and FDA. The current SwissPAR relating to the clinical pharmacology and clinical aspects refers to the publicly available Assessment Reports:
EMA Assessment Report EMA/686622/2019 (dated 14 November 2019)
FDA Medical Review Sunosi (date completed: 19 March 2019)

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Sunosi, film-coated tablets, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

SUNOSI®

Composition

Active substances

Solriamfetol hydrochloride

Excipients

Hydroxypropylcellulose, Magnesium stearate
Film coating: Poly(vinyl alcohol), Macrogola, Talc, Titanium dioxide (E 171), Iron oxide yellow (E 172)

Pharmaceutical form and active substance quantity per unit

SUNOSI 75 mg film-coated tablets
Yellow to dark yellow oblong tablet, with “75” debossed on one side and a score line on the opposite side, divisible.
1 film-coated tablet contains 89.25 mg solriamfetol hydrochloride equivalent to 75 mg of solriamfetol.
SUNOSI 150 mg film-coated tablets
Yellow oblong tablet, with “150” debossed on one side.
1 film-coated tablet contains 178.50 mg solriamfetol hydrochloride, equivalent to 150 mg of solriamfetol.

Indications/Uses

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.
SUNOSI is indicated to improve wakefulness and reduce excessive sleepiness in adult patients with narcolepsy.

Limitations of use

SUNOSI is not indicated for a causal treatment (primary therapy) of underlying airway obstruction in OSA. Prior to treatment of excessive daytime sleepiness with SUNOSI, primary OSA therapy (e.g., CPAP) must have been instituted for an adequate duration or, at the very least, attempted. Primary OSA therapy is to be maintained during treatment with SUNOSI. SUNOSI is not a replacement for primary OSA therapy."

Dosage/Administration

Treatment should be initiated by a healthcare professional experienced in the treatment of narcolepsy or OSA.
SUNOSI 75 mg film-coated tablets with "75" debossed on one side and a score line on the opposite side. Administration of a 37.5 mg dose can be achieved by halving a 75 mg tablet using the score line.
SUNOSI 150 mg film-coated tablets with "150" debossed on one side.

SUNOSI can be taken with or without food. Taking SUNOSI less than 9 hours before bedtime should be avoided as it may affect nighttime sleep.

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 after an interval of at least 3 days, with a recommended maximum daily dose of 150 mg once daily.

OSA

SUNOSI is not a therapy for the underlying airway obstruction in patients with OSA. Primary OSA therapy should be maintained in these patients.
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.
Long-term use: The need for continued treatment and the appropriate dose should be periodically assessed during extended treatment in patients prescribed SUNOSI.

Patients with impaired renal function

Mild renal impairment (creatinine clearance 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 7 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): SUNOSI is not recommended for use in patients with end stage renal disease.

Patients with impaired hepatic function
No dosage adjustment is required.

Elderly patients

Of the total number of patients in the narcolepsy and OSA clinical studies treated with SUNOSI, 13% (125/935) were 65 years of age or over.

No clinically meaningful differences in safety or effectiveness were observed between elderly and younger patients.

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.

Children and adolescents

The safety and efficacy of SUNOSI in children and adolescents (<18 years old) have not yet been established.
Clinical studies of SUNOSI in pediatric patients have not been conducted.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section “Excipients”.
- Concomitant use of monoamine oxidase inhibitors (MAOI) or within 14 days after MAOI treatment has been discontinued (see section “Interactions”).
- Myocardial infarction within the past year, unstable angina pectoris, uncontrolled hypertension, serious cardiac arrhythmias and other serious heart problems. SUNOSI has not been evaluated in patients with serious heart problems (see section “Warnings and Precautions”)

Warnings and precautions

Psychiatric symptoms

SUNOSI 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 SUNOSI should be carefully monitored for adverse reactions such as anxiety, insomnia and irritability, which may exacerbate pre-existing psychiatric disorders or symptoms. 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 SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose dependent fashion.

In the 12-week controlled trials in narcolepsy and OSA, mean changes across the day in blood pressure and heart rate relative to placebo were dose-dependent across the 37.5, 75 and 150 mg dose range. In narcolepsy patients, the mean changes from baseline to week 12 ranged from -1.2 to -0.1 mmHg for systolic blood pressure, 1.0 to 1.8 mmHg for diastolic blood pressure, and -0.3 to 1.6 bpm for heart rate. In OSA patients, the mean changes from baseline to week 12 ranged from 0.6 to 1.9 mmHg for systolic blood pressure, 0.1 to 0.7 mmHg for diastolic blood pressure, 0.5 to 2.2 bpm for heart rate. Individual blood-pressure or heart rate changes beyond these mean ranges were observed.

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 SUNOSI.

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of Major Adverse Cardiovascular Event (MACE), particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate (see “Interactions”).

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Abuse

SUNOSI was assessed in a human abuse potential study and demonstrated low abuse potential. Results from this clinical study demonstrated that SUNOSI 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 substance abuse, and these patients should be monitored for signs of misuse or abuse of SUNOSI.

Dependence

In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of SUNOSI were evaluated following at least 6 months of SUNOSI use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of SUNOSI were also evaluated during the two-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of SUNOSI resulted in a consistent pattern of adverse events in individual subjects that was suggestive of physical dependence or withdrawal.

Angle closure glaucoma

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

Interactions

No interaction studies have been performed (see section “Pharmacokinetic interactions”).
Concomitant use of medicinal products that increase blood pressure and heart rate should be used with caution (see section “Warnings and precautions”).
SUNOSI 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 “Contraindications”).
Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with SUNOSI. Interactions with dopaminergic drugs have not been evaluated with SUNOSI. Use caution when concomitantly administering dopaminergic drugs with SUNOSI.

Pharmacokinetic interactions

Clinical drug interaction studies with solriamfetol have not been conducted.
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 (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) and does not induce CYP enzymes 1A2, 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, MATE2-K, 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.

Pregnancy, lactation

Pregnancy

Women of childbearing potential and their male partners must use effective contraception during the use of Solriamfetol.
There are no or limited amount of data from the use of solriamfetol in pregnant women. Animal studies have shown maternal as well as embryo and fetal toxicity and teratogenic effects in rats and rabbits (see "Preclinical data"). As the potential risk for humans is not known, SUNOSI is not to be used during pregnancy and in women of childbearing potential not using contraception.

Lactation

It is unknown whether Solriametol is excreted in breast milk in humans. Animal studies have shown excretion of solriamfetol in milk. A risk to the newborns/infants cannot be excluded. SUNOSI should not be used during lactation.

Fertility

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

Effects on ability to drive and use machines

SUNOSI has a minor influence on the ability to drive and use machines.

Patients with abnormal levels of sleepiness, who take SUNOSI, should be advised that their level of wakefulness may not return to normal. Patients with excessive daytime sleepiness, including those taking SUNOSI, 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.

Undesirable effects

Summary of the safety profile

The safety of SUNOSI has been evaluated in 935 patients (ages 18 to 75 years) with narcolepsy or OSA. Among these patients, 396 were treated with SUNOSI in the 12-week placebo-controlled trials at doses of 37.5 mg (OSA only), 75 mg, and 150 mg once daily. Information provided below is based on the pooled 12-week placebo-controlled studies in patients with narcolepsy or OSA.

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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 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 specific adverse reactions and additional information

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.

Dose-dependent adverse reactions

In the 12-week clinical trials that compared doses of 37.5 mg, 75 mg and 150 mg/day of SUNOSI 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.

Discontinuation of treatment

In the 12-week placebo-controlled clinical trials, 11 of the 396 patients (3%) who received SUNOSI discontinued because of an adverse reaction compared to 1 of the 226 patients (<1%), who received placebo. The adverse reactions resulting in discontinuation that occurred in more than one SUNOSI-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

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

Signs and symptoms

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.

Treatment

A specific reversal agent for SUNOSI is not available. Hemodialysis removed approximately 21% of a 75 mg dose in end stage renal disease patients. In the case of inadvertent overdose, symptomatic and supportive medical care should be provided and patients should be carefully monitored, as appropriate.

Properties/Effects

ATC code

N06BA14

Mechanism of action

The mechanism of action of solriamfetol to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea is unclear. However, its efficacy is likely mediated through its activity as a dopamine and norepinephrine reuptake inhibitor (DNRI).

Pharmacodynamics

Pharmacodynamics 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. Solriamfetol has no appreciable binding affinity for the serotonin transporter (Ki=81.5 µM) and does not inhibit serotonin reuptake (IC_{50} > 100 µM). Solriamfetol binds to 5HT1A receptors and alpha-2A and alpha-2B adrenoceptors. Binding to 5HT1A receptors is associated with low potency agonist activity; however, binding to alpha 2A and alpha 2B receptors is not associated with functional activity as measured in cell-based *in vitro* assays. Solriamfetol has no appreciable binding affinity for dopamine, serotonin, norepinephrine, GABA, adenosine, histamine, orexin, benzodiazepine, muscarinic acetylcholine, or nicotinic acetylcholine receptors.

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.

Cardiac Electrophysiology

The effect of SUNOSI on the QT/QTcF interval was investigated in healthy volunteers. At a supratherapeutic dose 6 times the maximum recommended dosage, SUNOSI does not prolong the QTcF interval to a clinically relevant extent.

Clinical efficacy

Narcolepsy

Study 1, a 12-week, randomised, double-blind, placebo-controlled, parallel-group study, evaluated the efficacy of SUNOSI 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. 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, a total of 239 patients with narcolepsy were randomized to receive SUNOSI 75 mg, 150 mg, or 300 mg (two times the maximum recommended daily dose), or placebo once daily. Patients randomized to the 150-mg dose received 75 mg for the first 3 days before increasing to 150 mg. At Week 12, patients randomised to the 150 mg dose showed statistically significant improvements on the MWT (treatment effect difference: 7.7 minutes) and ESS (treatment effect difference: 3.8 points), 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. These effects were dose-dependent, observed at Week 1 and maintained over the study duration. 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 had less severe sleepiness. At Week 12, patients who were randomised to receive 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 Functional Outcomes of Sleep Questionnaire Short Version (FOSQ-10).

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

OSA

The efficacy of SUNOSI in improving wakefulness and reducing excessive daytime sleepiness in patients with OSA was demonstrated in a 12-week multi-center, randomized, double-blind, placebo-controlled study (Study 2) in adults diagnosed with OSA. The co-primary efficacy endpoints were change from baseline in MWT and ESS at Week 12. A pre-specified secondary endpoint was percentage of subjects reported as improved (minimally, much, or very much) at Week 12 by PGIc.

A total of 476 patients with OSA were randomized to receive solriamfetol 37.5 mg, 75 mg, 150 mg, 300 mg, or placebo once daily. At Week 12, patients randomized to the 75 mg and 150 mg dose arms showed statistically significant improvements on the co-primary endpoints of MWT (treatment effect difference: 8.9 minutes and 10.7 minutes respectively) and ESS (treatment effect difference: 1.7 points and 4.5 points respectively) as well as on the PGIc (key secondary endpoint), compared with placebo. Patients randomized to 37.5 mg solriamfetol showed statistically significant improvements based on the MWT (treatment effect difference of 4.5 min) and ESS (treatment effect difference of 1.9 points) compared to placebo. These effects were observed at Week 1, maintained over the study duration and were dose-dependent. The change on percentage of subjects reported as improved by PGIc was also statistically significant compared with placebo at the 75 mg and 150 mg doses. Dose-dependent improvements in the ability to conduct daily activities were observed, as measured by the FOSQ-10.

Demographic and baseline disease characteristics were similar for the SUNOSI and placebo groups. Median age was 55 years (range 20 to 75 years), 37% were female, 76% were Caucasian, 19% were African American, and 4% were Asian.

Nighttime sleep as measured with polysomnography was not affected by the use of SUNOSI in Study 2. Patients' compliance with a primary OSA therapy device was similar across the placebo and SUNOSI treatment groups at baseline, and did not change during the 12-week study period in any treatment group.

Long-term data

The maintenance of effect of SUNOSI in improving wakefulness and reducing excessive daytime sleepiness in patients with narcolepsy and OSA was assessed in two randomized-withdrawal, placebo-controlled studies.

Study 3 was a 6-week, multi-center, double-blind, placebo-controlled, randomized-withdrawal study in 174 adult patients with a diagnosis of OSA. The co-primary efficacy endpoints were change from the beginning to the end of the randomized withdrawal period in MWT and ESS. During a 2-week, open-

label titration phase, patients were started on SUNOSI 75 mg once daily, and were titrated to the maximum tolerable dose between 75 mg and 300 mg per day. Patients were continued on this dose for a 2-week stable-dose phase. At the end of the stable-dose phase, 124 patients who reported “much” or “very much” improvement on the PGIc and who showed improvements on the MWT and ESS entered a double-blind withdrawal phase and were randomized 1:1 to either continue SUNOSI at the dose received in the stable-dose phase or switch to placebo. Compared to patients who remained on SUNOSI, patients randomized to placebo experienced statistically significant worsening of sleepiness as measured by the MWT and ESS.

Study 4 was a 52-week, open-label study in 638 patients with either narcolepsy or OSA, who had completed a prior trial. During a 2-week, open-label titration phase, patients were started on SUNOSI 75 mg once daily, and were titrated to the maximum tolerable dose between 75 mg and 300 mg per day. Patients remained on this dose during a subsequent open-label treatment period of either 38 (for patients previously enrolled in Study 1 and 2) or 50 (all others) weeks. A 2-week randomized-withdrawal period was incorporated into the study. After 6 months of stable-dose treatment, 282 patients (79 with narcolepsy; 203 with OSA) entered the randomized-withdrawal period. Patients were randomized 1:1 to either continue to receive SUNOSI at the dose received in the maintenance phase or to switch to placebo. The primary efficacy endpoint was change from the beginning to the end of the randomized-withdrawal period in ESS. Patients treated with SUNOSI. remained improved, whereas placebo-treated patients worsened (LS mean difference of -3.7 on ESS; $p<0.0001$) during the randomized-withdrawal period after at least 6 months of open-label treatment. Fewer patients treated with SUNOSI reported worsening on the PGIc (percentage difference of -36.2%; $p<0.0001$).

Study 4 results demonstrated long-term maintenance of efficacy with continued SUNOSI 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.

Pharmacokinetics

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}.

Distribution

The apparent volume of distribution of solriamfetol is approximately 199 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.

Metabolism

Solriamfetol is minimally metabolised in humans.

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 dose range of 42 to 1008 mg (approximately 0.28 to 6.7 times the maximum recommended dosage). Steady state is reached within 3 days, and once-daily administration 150 mg is expected to result in minimal solriamfetol accumulation (1.06 times single-dose exposure) with C_{max} and AUC_{tau} values of 835 ng/mL and 8874 ng*hr/mL, respectively.

Kinetics in specific patient groups

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

Children and adolescents

The use of Solriamfetol has not been studied in children and adolescents.

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, and $t_{1/2}$ increased at least 13-fold in patients with end stage renal disease (ESRD) without hemodialysis and in patients with ESRD undergoing hemodialysis. SUNOSI is not recommended for use in patients with ESRD. In patients with ESRD, an average of 21% of solriamfetol was removed by hemodialysis.

Hepatic impairment

No dosage adjustment is necessary.

Preclinical data

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

Repeated dose toxicity

Repeated dose toxicity studies with daily oral application were conducted in mice (duration 3 months, no-observed-adverse-effect level [NOAEL] 17 mg/kg/day), rats (duration 6 months with a 3-month recovery period, NOAEL not established, lowest-observed-adverse-effect level [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.

Carcinogenicity

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.

Reproductive toxicity

Embryofetal development

Possible effects on embryofetal development were investigated in pregnant rats and rabbits. In both species embryofetal toxicity (increased postimplantation loss in rats, increased incidence of skeletal anomalies that included sternebrae malalignment, hindlimb rotation, bent limb bones, and situs inversus in rats and sternebrae malalignment in rabbits, and decreased fetal weights in both species) was only evident in the presence of maternal toxicity (decreased body weights in both species). Whether embryotoxicity was a consequence of maternal toxicity or a direct effect of solriamfetol cannot be determined. In a distribution study in pregnant rats ^{14}C-solriamfetol was detected in fetal membrane (approximately twice as high as in blood), placenta and whole fetus (nearly similar to blood concentration) and thus a direct toxic effect on the fetus cannot be excluded. In rats the exposure margins at the maternal and developmental NOAEL are below the human exposure (0.6 – 0.7 times 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.

Other data

Studies on juvenile animals

In a pivotal toxicity study in young rats, solriamfetol was administered by oral gavage once daily from postnatal day 21 to 111. Mortality, mild clinical signs, reduced body weights and reduced body weight gains, reduced food consumption, delayed sexual maturation in females, and increased serum phosphorus levels at the end of the dosing and an 10 week recovery period were observed. There were no solriamfetol-related effects on behavioral assessments, estrous cycling, mating and fertility, ophthalmologic examinations, hematology or coagulation, gross necropsy findings, ovarian and uterine examinations, sperm evaluations, organ weights, femur lengths or histopathology. A detailed neuropathological evaluation revealed no changes in brain weights, gross brain measurements, brain morphometric measurements, histopathologic findings in the brain, spinal cord, cranial nerves, dorsal root ganglia, dorsal and ventral spinal nerves, peripheral nerves, skeletal muscle, or eyes. As regards general toxicity, the no-effect dose for adverse effects (NOAEL) in juvenile rats is associated with

plasma exposures (AUC) in humans about 2 times that measured at the MRHD. The rat-to-human exposure (AUC) ratios at the no-observed adverse effect level for growth and development are about 24 and 2.4 for males and females, respectively.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 25°C.
Keep out of the reach of children.

Instructions for handling

No special requirements for disposal.

Authorisation number

68177 (Swissmedic)

Packs

SUNOSI 75 mg: Pack with 28 film-coated tablets (divisible) [B]
SUNOSI 150 mg: Pack with 28 film-coated tablets [B]

Marketing authorisation holder

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