Applicant: Teva Pharmaceuticals (Pty) Ltd	**Product: NUVIGIL 50; 150 & 250 mg tablets**
Date of Registration: 20 April 2021 **NUVIGIL 50 mg: 48/1.1/1129** **NUVIGIL 150 mg: 48/1.1/1130** **NUVIGIL 250 mg: 48/1.1/1131**	Each tablet contains 50; 150 or 250 mg armodafinil respectively
SAHPRA approved: 15.11.2024	

PROFESSIONAL INFORMATION

Applicant: Teva Pharmaceuticals (Pty) Ltd	Product: NUVIGIL 50; 150 & 250 mg tablets
Date of Registration: 20 April 2021 **NUVIGIL 50 mg: 48/1.1/1129** **NUVIGIL 150 mg: 48/1.1/1130** **NUVIGIL 250 mg: 48/1.1/1131**	Each tablet contains 50; 150 or 250 mg armodafinil respectively
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SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE:

NUVIGIL 50 mg (Tablets)

NUVIGIL 150 mg (Tablets)

NUVIGIL 250 mg (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

NUVIGIL 50 mg: Each tablet contains 50 mg armodafinil as active substance.

NUVIGIL 150 mg: Each tablet contains 150 mg armodafinil as active substance.

NUVIGIL 250 mg: Each tablet contains 250 mg armodafinil as active substance.

Excipients with known effect:

NUVIGIL 50 mg contains 35,9 mg lactose monohydrate.

NUVIGIL 150 mg contains 107,7 mg lactose monohydrate.

NUVIGIL 250 mg contains 179,5 mg lactose monohydrate.

For the full list of excipients, see **section 6.1**.

Applicant: Teva Pharmaceuticals (Pty) Ltd	Product: NUVIGIL 50; 150 & 250 mg tablets
Date of Registration: 20 April 2021 **NUVIGIL 50 mg: 48/1.1/1129** **NUVIGIL 150 mg: 48/1.1/1130** **NUVIGIL 250 mg: 48/1.1/1131**	Each tablet contains 50; 150 or 250 mg armodafinil respectively
SAHPRA approved: 15.11.2024	

3. PHARMACEUTICAL FORM:

Tablets.

NUVIGIL 50 mg: Round, white to off-white tablet, debossed with Cephalon ‘C’ on one side and ‘205’on the other side.

NUVIGIL 150 mg: Oval, white to off-white tablet, debossed with Cephalon ‘C’ on one side and ‘215’ on the other side.

NUVIGIL 250 mg: Oval, white to off-white tablet, debossed with Cephalon ‘C’ on one side and ‘225’ on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

NUVIGIL is indicated:

- to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy.

4.2 Posology and method of administration:

Posology:

NUVIGIL (armodafinil) is for oral administration.

NUVIGIL should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of the underlying disorder of narcolepsy has been made in accordance with International Classification of Sleep Disorders (ICSD) or Diagnostic and Statistical Manual (DSM) diagnostic criteria. Such an evaluation usually consists of a complete history and physical examination, and it may be supplemented with testing in a laboratory setting.

NUVIGIL may be taken with or without food, however administration with food may delay the onset of action and prolong the effect of the medicine (see **section 5.2**).

To avoid a delayed onset of action NUVIGIL should be taken on an empty stomach.

Treatment with NUVIGIL should be initiated and supervised by medical practitioners with appropriate experience in the treatment of narcolepsy and who have access to sleep laboratory diagnostic facilities.

Narcolepsy:

The recommended dose of NUVIGIL for patients with narcolepsy is 150 mg or 250 mg given once daily in the morning.

Dosing in special populations:

The dose of NUVIGIL should be reduced in patients with severe (Child-Pugh class C) hepatic impairment, with or without cirrhosis (see **section 5.2**). There is a lack of data on dosing instruction for NUVIGIL (armodafinil) specific to the degree of liver impairment.

There is inadequate information to determine safety and efficacy of dosing of NUVIGIL

(armodafinil) in patients with mild, moderate or severe renal impairment (see **section 5.2**).

There is insufficient information to recommend a safe and effective dose in severe renal impairment (CrCl less than 20 ml/min).

In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore reduction of NUVIGIL doses and patients close monitoring should be considered (see **section 5.2, Special Populations**).

When changing treatment from modafinil, systemic exposure to NUVIGIL (armodafinil) at steady state was approximately 40 % and 70 % higher than modafinil as assessed by C_{max} and $AUC_{0-\tau}$, respectively. Therefore, although dose adjustment may allow for comparable C_{max} or $AUC_{0-\tau}$, equivalent exposure (as assessed by both parameters) cannot be achieved due to the nature of the observed differences in the overall profiles of armodafinil and modafinil.

4.3 Contraindications:

- Hypersensitivity to modafinil, armodafinil or any other ingredient listed in **section 6.1**.
- Patients who are pregnant or may become pregnant.
- Uncontrolled moderate to severe hypertension and in patients with cardiac dysrhythmias.

4.4 Special warnings and precautions for use:

Armodafinil is a single enantiomer of racemic modafinil. The two enantiomers of modafinil have different pharmacokinetics. The half-life of armodafinil, the (R)-enantiomer, is approximately three times that of the (S)-enantiomer in adult humans. The implications of the pharmacokinetic differences between the medicines on the duration of clinical action remain unelucidated. No evidence of interconversion of the (R)- and (S)-enantiomers of modafinil have been observed *in vitro* or *in vivo*. Thus, armodafinil and modafinil are not bioequivalent, and therefore are not directly substitutable, (see **section 4.2**).

Serious rash, including Stevens-Johnson Syndrome:

Serious rash requiring hospitalisation and discontinuation of treatment has been reported in adults in association with the use of NUVIGIL (armodafinil) and modafinil [the racemic mixture of (S)- and (R)-enantiomers].

NUVIGIL has not been studied in paediatric patients in any setting and is not approved for use in paediatric patients.

In clinical trials of modafinil (the racemate), the incidence of rash resulting in discontinuation was approximately 0,8 % (13 per 1 585) in paediatric patients (age <17 years); these rashes included 1 case of possible Stevens-Johnson Syndrome (SJS) and 1 case of apparent multi-organ hypersensitivity reaction. Several of the cases were associated with fever and other abnormalities (e.g., vomiting, leukopenia). The median time to rash that resulted in discontinuation was 13 days. No such cases were observed among 380 paediatric patients who received placebo. No serious skin rashes have been reported in adult clinical trials (0 per 4 264) of modafinil. Cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in adults in worldwide post-marketing experience. The

reporting rate of TEN and SJS associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate. Estimates of the background incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.

Cases of serious rash similar to those observed with modafinil including skin and mouth blistering have been reported in adults in post-marketing experience with NUVIGIL.

One fatal case of DRESS occurred in close temporal association (3 weeks) with the initiation of NUVIGIL treatment.

There are no factors that are known to predict the risk of occurrence or the severity of rash associated with NUVIGIL or modafinil. Nearly all cases of serious rash associated with these medicines occurred within 1 to 5 weeks after treatment initiation. However, isolated cases have been reported after prolonged treatment (e.g. 3 months). Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes also occur with NUVIGIL, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, NUVIGIL should be discontinued at the first sign of rash, unless the rash is clearly not medicine related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

Angioedema and anaphylactoid reactions:

Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm), were observed with NUVIGIL. Patients should be advised to discontinue therapy and immediately report to their medical practitioner any signs or symptoms suggesting angioedema or anaphylaxis (e.g., swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).

Multi-organ hypersensitivity reactions:

Multi-organ hypersensitivity reactions, including at least one fatality in post marketing experience, have occurred in close temporal association (median time to detection 13 days: range 4-33) to the initiation of modafinil. A similar risk of multi-organ hypersensitivity reactions with NUVIGIL cannot be ruled out.

Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalisation or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included myocarditis, hepatitis, liver function test abnormalities, haematological abnormalities (e.g., eosinophilia, leukopenia, thrombocytopenia), pruritus, and asthenia. Because multi-organ hypersensitivity is variable in its expression, other organ system symptoms and signs, not noted here, may occur.

If a multi-organ hypersensitivity reaction is suspected, NUVIGIL should be discontinued. Although there are no case reports to indicate cross-sensitivity with other medicines that produce this syndrome, the experience with medicines associated with multi-organ hypersensitivity would indicate this to be a possibility.

Persistent sleepiness:

Patients with abnormal levels of sleepiness who take NUVIGIL should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking NUVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised

to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

Psychiatric symptoms:

In narcolepsy controlled trials of NUVIGIL, anxiety, agitation, nervousness, and irritability were reasons for treatment discontinuation more often in patients on NUVIGIL compared to placebo (NUVIGIL 1,2 % and placebo 0,3 %). Depression was also a reason for treatment discontinuation more often in patients on NUVIGIL compared to placebo (NUVIGIL 0,6 % and placebo 0,2 %). Cases of suicide ideation were observed in clinical trials.

Caution should be exercised when NUVIGIL is given to patients with a history of psychosis, depression, or mania. If psychiatric symptoms develop in association with NUVIGIL administration, NUVIGIL should be discontinued.

Psychiatric adverse experiences have been reported in patients treated with modafinil. Modafinil and armodafinil (NUVIGIL) are very closely related. Therefore, the incidence and type of psychiatric symptoms associated with NUVIGIL are expected to be similar to the incidence and type of these events with modafinil.

Post-marketing adverse events associated with the use of modafinil have included mania, delusions, hallucinations, suicidal ideation and aggression, some resulting in hospitalisation. Post-marketing adverse reactions associated with the use of NUVIGIL have included suicidal ideation, aggression, and also cases of mania, delusions and hallucinations, some resulting in hospitalisation. Many, but not all, patients had a prior psychiatric history. One healthy male volunteer developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of

modafinil and sleep deprivation. There was no evidence of psychosis 36 hours after medicine discontinuation.

Cardiovascular system:

NUVIGIL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable angina pectoris, and such patients should be treated with caution.

In clinical studies of modafinil, cardiovascular adverse events, including chest pain, palpitations, dyspnoea and transient ischaemic T-wave changes on ECG were observed in three subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that NUVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving central nervous system (CNS) stimulants. Findings suggestive of mitral valve prolapse syndrome include, but are not limited to, ischaemic ECG changes, chest pain, or dysrhythmia. If new onset of any of these symptoms occurs, consider cardiac evaluation.

Blood pressure monitoring in short-term (≤3 months) controlled trials of narcolepsy showed small average increases in mean systolic and diastolic blood pressure in patients receiving NUVIGIL as compared to placebo (1,2 to 4,3 mmHg in the various experimental groups). There was also a slightly greater proportion of patients on NUVIGIL requiring new or increased use of antihypertensive medicines (2,9 %) compared to patients on placebo (1,8 %). There was a consistent, average increase in pulse rate over placebo in controlled trials. This increase varied from 0,9 to 3,5 BPM. Increased monitoring of heart rate and blood pressure may be appropriate in patients on NUVIGIL. Caution should be exercised when prescribing NUVIGIL to patients with known cardiovascular disease.

Patients (Women) using contraception:

Sexually active women of child-bearing potential should be established on a contraceptive program before taking NUVIGIL.

The effectiveness of steroidal contraceptives may be reduced when used with NUVIGIL and for two months after discontinuation of therapy (see **section 4.5**). Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptive (e.g., Ethinylestradiol) when treated concomitantly with NUVIGIL and for two months after discontinuation of NUVIGIL treatment.

Abuse and dependence potential:

Although the abuse potential of NUVIGIL has not been specifically studied, its abuse potential is likely to be similar to that of modafinil.

In humans, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking and feelings typical of other CNS stimulants. In *in vitro* binding studies, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. Modafinil is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies, modafinil was also partially discriminated as stimulant-like. Medical practitioners should follow patients closely, especially those with a history of drug and/or stimulant (e.g., methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (e.g., incrementation of doses or drug-seeking behaviour).

The abuse potential of modafinil (200, 400, and 800 mg) was assessed relative to methylphenidate (45 and 90 mg) in an inpatient study in individuals experienced with drugs of abuse. Results from this clinical study demonstrated that modafinil produced psychoactive and euphoric effects and feelings

consistent with other scheduled CNS stimulants (methylphenidate).

Use in hepatic impairment:

The dose of NUVIGIL should be reduced in patients with severe (Child-Pugh class C) hepatic impairment, with or without cirrhosis (see **sections 5.2** and **4.2**). There is a lack of data on dosing instruction for NUVIGIL (armodafinil) specific to the degree of liver impairment.

Use in renal impairment:

There is inadequate information to determine safety and efficacy of NUVIGIL (armodafinil) dosing in patients with mild, moderate or severe renal impairment. (See **sections 5.2** and **4.2**). There is insufficient information to recommend a safe and effective dose in severe renal impairment (CrCl less than 20 ml/min).

Use in the elderly:

In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, the dose of NUVIGIL and elderly patients should be closely monitored (see **section 4.2**).

Paediatric use:

There is a lack of either safety or efficacy data for use in paediatric populations (see Serious Rash, including Stevens-Johnson Syndrome). Serious rash has been seen in paediatric patients receiving modafinil. NUVIGIL is not for use in patients < 18 years of age.

Effect on laboratory tests:

Clinical chemistry, haematology, and urinalysis parameters were monitored in the studies. Mean plasma levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (AP) were found to be

higher following administration of NUVIGIL, but not placebo. Few subjects, however, had GGT or AP elevations outside of the normal range. No differences were apparent in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, or total bilirubin, although there were rare cases of isolated elevations of AST and/or ALT. A single case of mild pancytopenia was observed after 35-days of treatment and resolved with medicine discontinuation. A small mean decrease from baseline in serum uric acid compared to placebo was seen in clinical trials. The clinical significance of this finding is unknown.

NUVIGIL contains sugar (lactose monohydrate). Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take NUVIGIL.

4.5 Interaction with other medicines and other forms of interaction:

In vitro data demonstrated that NUVIGIL weakly induces CYP1A2 and possibly CYP3A activities in a concentration-related manner and that CYP2C19 activity is reversibly inhibited by NUVIGIL. *In vivo,* CYP2B6 was induced by NUVIGIL. Other CYP activities did not appear to be affected by NUVIGIL. An *in vitro* study demonstrated that NUVIGIL is a substrate of P-glycoprotein.

Potential interactions with medicines that inhibit, induce, or are metabolised by cytochrome P450 isoenzymes and other hepatic enzymes:

The existence of multiple pathways for NUVIGIL metabolism, as well as the fact that a non-CYP-related pathway is the most rapid in metabolising NUVIGIL, suggest that there is a low probability of substantive effects on the overall pharmacokinetic profile of NUVIGIL due to CYP inhibition by concomitant medicines. However, due to the partial involvement of CYP3A enzymes in the metabolic elimination of NUVIGIL, co-administration of potent inducers of CYP3A4/5 (e.g., carbamazepine, oxcarbazepine, phenobarbitone, phenytoin, rifabutin, rifampicin and St. John's wort) or inhibitors of CYP3A4/5 (e.g.: protease inhibitors [e.g. ritonavir, indinavir, nelfinavir, saquinavir], clarithromycin, erythromycin, chloramphenicol, ketoconazole, itraconazole, nefazodone, diltiazem and verapamil) could alter the plasma concentrations of NUVIGIL.

The potential of NUVIGIL to alter the metabolism of other medicines by enzyme induction or inhibition:

Medicines metabolised by CYP3A4/5:

In vitro data demonstrated that the NUVIGIL (armodafinil) metabolite modafinil sulfone, is a weak inducer of CYP3A activity. In a clinical study, concomitant administration of NUVIGIL 250 mg resulted in a reduction in systemic exposure to midazolam by 32 % after a single oral dose (5 mg) and 17 % after a single intravenous dose (2 mg). Therefore, the blood levels and effectiveness of medicines that are substrates for CYP3A enzymes (e.g., steroidal contraceptives, ciclosporin,

midazolam, and triazolam) may be reduced after initiation of concomitant treatment with NUVIGIL, and dose adjustment may be required.

In a clinical study the concomitant administration of NUVIGIL 250 mg with carbamazepine (400 mg/day) resulted in a reduction in the mean systemic exposure of carbamazepine by approximately 25 %. Carbamazepine dose adjustment may be required when co-administered with NUVIGIL, particularly when starting or stopping co-administration of the two medicines.

In a separate clinical study, concomitant administration of NUVIGIL 250 mg with quetiapine (300 mg to 600 mg daily doses) resulted in a reduction in the mean systemic exposure of quetiapine by approximately 29 %. No dose adjustment is required.

The blood levels of ciclosporin may be reduced when used with NUVIGIL. Monitoring of circulating ciclosporin concentrations and appropriate dosage adjustment for ciclosporin should be considered when these medicines are used concomitantly.

Medicines metabolised by CYP1A2:

In vitro data demonstrated that NUVIGIL and its metabolite modafinil sulfone are weak inducers of CYP1A2 in a concentration-related manner. However, in a clinical study using caffeine as a probe substrate, no significant effect on CYP1A2 activity was observed.

Medicines metabolised by CYP2C19:

In vitro data demonstrated that NUVIGIL, and more so its metabolite modafinil sulfone, are reversible inhibitors of CYP2C19 activity. In a clinical study, concomitant administration of NUVIGIL 400 mg resulted in a 40 % increase in exposure to omeprazole after a single oral dose (40 mg), as a result of moderate inhibition of CYP2C19 activity. Therefore, dose reduction may be required for some medicines that are substrates for CYP2C19 (e.g., phenytoin, diazepam, propranolol,

omeprazole, esomeprazole and clomipramine) when used concomitantly with NUVIGIL.

Medicines metabolised by CYP2B6:

In vitro data demonstrated that racemic modafinil is a weak inducer of CYP2B6 activity in a concentration-related manner.

Interactions with CNS active medicines:

Concomitant administration of NUVIGIL with quetiapine reduced the systemic exposure of quetiapine.

Data specific to NUVIGIL medicine interaction potential with other CNS active medicines are not available. However, the following available interaction information on modafinil should be applicable to NUVIGIL.

Concomitant administration of modafinil with methylphenidate or dextroamphetamine produced no significant alterations on the pharmacokinetic profile of modafinil or either stimulant, even though the absorption of modafinil was delayed for approximately one hour.

Concomitant modafinil or clomipramine did not alter the pharmacokinetic profile of either medicine; however, one incident of increased levels of clomipramine and its active metabolite desmethylclomipramine was reported in a patient with narcolepsy during treatment with modafinil.

Data specific to NUVIGIL or modafinil medicine interaction potential with monoamine oxidase (MAO) inhibitors are not available. Therefore, caution should be used when concomitantly administering MAO inhibitors and NUVIGIL.

Interaction with P-Glycoprotein:

An *in vitro* study demonstrated that armodafinil is a substrate, but not inhibitor, of P-glycoprotein.

The clinical impact of inhibition of P-glycoprotein on the bioavailability of armodafinil is not known.

Interactions with other medicines:

Data specific to NUVIGIL medicine interaction potential for additional other medicines are not available. However, the following available interaction information on modafinil should be applicable to NUVIGIL.

Concomitant administration of modafinil with warfarin did not produce significant changes in the pharmacokinetic profiles of (R)- and (S)-warfarin. However, since only a single dose of warfarin was tested in this study, an interaction cannot be ruled out. Therefore, more frequent monitoring of prothrombin times/INR should be considered whenever NUVIGIL is co-administered with warfarin.

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential/Contraception in males and females:

Sexually active women of child-bearing potential must be on an effective contraceptive program before and while taking NUVIGIL and for two months after discontinuation of therapy (see **section 4.5**).

As NUVIGIL may reduce the effectiveness of oral contraception alternative additional methods of contraception are required (see **sections 4.4** and **4.5**).

Pregnancy:

NUVIGIL is contraindicated during pregnancy (see **section 4.3**).

NUVIGIL taken during pregnancy has been associated with serious foetal abnormalities such as cardiac lesions and microcephaly. In addition intrauterine growth restriction and spontaneous abortion has been reported in association with NUVIGIL and modafinil in humans.

A woman should not commence NUVIGIL until two reliable pregnancy tests have shown negative results one week apart.

Patients should be cautioned regarding the potential increased risk of pregnancy when using steroidal contraceptives with NUVIGIL and for two months after discontinuation of therapy (see **section 4.5**).

Modafinil and/or its metabolites cross the placenta in rats, but placental transfer of armodafinil *per se* has not been studied. In studies of armodafinil [(R)-modafinil] and modafinil [a mixture of (R)- and (S)-modafinil] conducted in rats (armodafinil, modafinil) and rabbits (modafinil), developmental toxicity was observed at clinically relevant plasma exposures.

Oral administration of armodafinil to pregnant rats and rabbits throughout organogenesis resulted in increased incidences of foetal structural alterations and foetal toxicity at the highest dose. The highest no-effect dose for embryo foetal developmental toxicity in rats was associated with a plasma

armodafinil exposure (AUC) less than that in humans at the maximum recommended human dose (MRHD) of NUVIGIL (250 mg/day).

Breastfeeding:

It is not known whether armodafinil or its metabolites are excreted in human milk. The effects of armodafinil on infants who have been breastfed have not been studied. Breastfeeding is not recommended during administration of NUVIGIL.

Modafinil and/or its metabolites including modafinil sulfone and modafinil acid have been found in the milk of lactating rats.

Infant growth retardation has been reported in association with NUVIGIL use during breastfeeding.

Fertility:

The effect of NUVIGIL on fertility is unknown.

4.7 Effects on ability to drive and use machines:

Patients taking NUVIGIL should be advised that their level of wakefulness may not return to normal. Patients should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Undesirable effects such as blurred vision or dizziness might also affect ability to drive (see **section 4.8**).

Family and caregivers should be aware that taking this medicine may not return the recipient to full wakefulness especially in relation to driving and the use of heavy machinery.

4.8 Undesirable effects:

a. Summary of the safety profile:

NUVIGIL has been evaluated for safety in over 1 100 patients.

In the controlled clinical trials, the most commonly observed adverse events (≥5 %) associated with the use of NUVIGIL occurring more frequently than in the placebo-treated patients were headache, nausea, dizziness, and insomnia. The adverse event profile was similar across the studies.

In the controlled clinical trials, 44 of the 645 patients (7 %) who received NUVIGIL discontinued due to an adverse experience compared to 16 of the 445 (4 %) of patients that received placebo. The most frequent reason for discontinuation was headache (1 %).

Incidence in Controlled Trials:

The following table (Table 1) presents the adverse experiences that occurred at a rate of 1 % or more and were more frequent in patients treated with NUVIGIL than in placebo group patients.

The prescriber should be aware that the figures provided below cannot be used to predict the frequency of adverse experiences in the course of usual medical practice, where patient characteristics and other factors may differ from those occurring during clinical studies.

b. Tabulated list of adverse reactions:

Table 1: Incidence 1 % or greater of treatment-emergent adverse experiences in parallel-group, placebo-controlled clinical trials with* NUVIGIL *(150 mg and 250 mg)*[1]*:*

SYSTEM ORGAN CLASS **MeDRA preferred term**	**NUVIGIL** **(percent,** **N=645)**	**PLACEBO** **(percent,** **N=445)**
Cardiac disorders:		
Palpitations	2	1
Gastrointestinal disorders:		
Nausea	7	3
Diarrhoea	4	2
Dry mouth	4	1
Dyspepsia	2	0
Upper abdominal pain	2	1
Constipation	1	0
Vomiting	1	0
Loose stools	1	0
General disorders and administration site conditions:		
Fatigue	2	1
Thirst	1	0
Influenza-like illness	1	0
Pain	1	0
Pyrexia	1	0
Immune system disorders:		

Seasonal allergy	1	0
Investigations:		
Increased gamma glutamyltransferase	1	0
Increased heart rate	1	0
Metabolism and nutrition disorders:		
Anorexia	1	0
Decreased appetite	1	0
Nervous system disorders:		
Headache	17	9
Dizziness	5	2
Disturbance in attention	1	0
Tremor	1	0
Migraine	1	0
Paraesthesia	1	0
Psychiatric disorders:		
Insomnia	5	1
Anxiety	4	1
Depression	2	0
Agitation	1	0
Nervousness	1	0
Depressed mood	1	0
Renal and urinary disorders:		
Polyuria	1	0
Respiratory, thoracic and mediastinal disorders:		
Dyspnoea	1	0

Skin and subcutaneous tissue disorders:		
Rash	2	0
Contact dermatitis	1	0
Hyperhidrosis	1	0

*Included are only those events for which NUVIGIL incidence is greater than that of placebo.

[1] Events for which the NUVIGIL incidence was at least 1 % but equal to or less than placebo are not listed in the table. The events included the following: flatulence, chest pain, bronchitis, nasopharyngitis, sinusitis, upper respiratory tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, arthralgia, back pain, oropharyngeal pain, cough and hypertension.

Dose dependency of adverse events:

In clinical trials which compared doses of 150 mg/day and 250 mg/day of NUVIGIL and placebo, the only adverse events that appeared to be dose-related were headache, rash, depression, dry mouth, insomnia, and nausea. See Table 2 for additional information.

Table 2: Incidence of dose-dependent, treatment-emergent adverse experiences by dose and by treatment in parallel-group, placebo-controlled clinical trials with* NUVIGIL *(150 mg and 250 mg):*

SOC MedDRA preferred term	**NUVIGIL 250 mg (%) N=198**	**NUVIGIL 150 mg (%) N=447**	**NUVIGIL Combined (%) N=645**	**Placebo (%) N=445**
Gastrointestinal disorders:				
Nausea	9	6	7	3
Dry Mouth	7	2	4	<1

Nervous system disorders:				
Headache	23	14	17	9
Psychiatric disorders:				
Insomnia	6	4	5	1
Depression	3	1	2	<1
Skin and subcutaneous tissue disorders:				
Rash	4	1	2	<1

Vital Sign Changes:

Blood pressure monitoring in controlled trials showed small average increases in mean systolic and diastolic blood pressure in patients receiving NUVIGIL as compared to placebo (1,2 to 4,3 mmHg in the various experimental groups). There was also a greater proportion of patients on NUVIGIL requiring new or increased use of antihypertensive medicines (2,9 %) compared to patients on placebo (1,8 %). There was a consistent, average increase in pulse rate over placebo. This increase varied from 0,9 to 3,5 BPM.

Table 3: Post-marketing experience:

Post marketing experience for NUVIGIL, principally from spontaneous reporting, has documented the following adverse events.

Cardiac disorders: Supraventricular dysrhythmias, myocardial infarction
Gastrointestinal disorders: Mouth sores (including mouth blistering and ulceration)
General disorders and administration site conditions: Feeling abnormal, irritability
Immune system disorders: Drug hypersensitivity, anaphylaxis
Nervous system disorders: Convulsions
Psychiatric disorders: Hallucination, anger, aggression, drug abuse, psychotic disorder, suicidal ideation, suicide attempt, mania
Respiratory, thoracic and mediastinal disorders: Throat tightness, pharyngeal oedema
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, alopecia, drug reaction with eosinophilia and systemic symptoms (DRESS)

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms of NUVIGIL overdose are likely to be central nervous system symptoms such as insomnia, restlessness, disorientation, confusion, agitation, anxiety, excitation and hallucination; digestive changes such as nausea and diarrhoea; and cardiovascular changes such as tachycardia, bradycardia, hypertension and chest pain and dyspnoea.

No specific antidote exists for the toxic effects of a NUVIGIL overdose. Treatment should be symptomatic and supportive including cardiovascular monitoring. There are no data to suggest the utility of dialysis or urinary acidification or alkalinisation in enhancing medicine elimination.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: A wakefulness-promoting agent. ATC code: N06BA13.

Mechanism of action:

The mechanism(s) through which armodafinil promotes wakefulness is unknown. Armodafinil [(R)-modafinil)] has pharmacological properties similar to those of modafinil [a mixture of (R)- and (S)-modafinil] to the extent tested in animal and *in vitro* studies. The (R)- and (S)-enantiomers have similar pharmacological actions in animals.

Armodafinil has a wake-promoting action similar to that of sympathomimetic medicines including amphetamine and methylphenidate, although their pharmacologic profile is different.

Armodafinil is an indirect dopamine receptor agonist; and armodafinil binds *in vitro* to the dopamine transporter and inhibits dopamine reuptake.

In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing properties, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like (see **section 4.4**). Armodafinil is likely to have similar actions.

Based on nonclinical studies, two major metabolites, armodafinil acid and armodafinil sulfone, of armodafinil, do not contribute to the CNS-activating properties of the parent compound.

Clinical trials:

The effectiveness of NUVIGIL in improving wakefulness has been established in narcolepsy.
For each clinical trial, a p-value of $\leq 0{,}05$ was required for statistical significance.

Narcolepsy:

The effectiveness of NUVIGIL in improving wakefulness in patients with excessive sleepiness (ES) associated with narcolepsy was established in one 12-week, multi-centre, placebo-controlled, parallel-group, double-blind study of outpatients who met the ICSD criteria for narcolepsy. A total of 196 patients were randomized to receive NUVIGIL 150 or 250 mg/day, or matching placebo. The ICSD criteria for narcolepsy include either:

- recurrent daytime naps or lapses into sleep that occur almost daily for at least three months, plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy), or
- a complaint of excessive sleepiness or sudden muscle weakness with associated features: sleep paralysis, hypnagogic hallucinations, automatic behaviours, disrupted major sleep episode; and polysomnography demonstrating one of the following: sleep latency less than 10 minutes or rapid eye movement (REM) sleep latency less than 20 minutes and a Multiple Sleep Latency Test (MSLT) that demonstrates a mean sleep latency of less than 5 minutes and two or more sleep onset REM periods and no medical or mental disorder accounts for the symptoms.

For entry into the study, all patients were required to have objectively documented excessive daytime sleepiness, via MSLT with a sleep latency of 6 minutes or less and the absence of any other clinically significant active medical or psychiatric disorder. The MSLT, an objective polysomnographic assessment of the patient's ability to fall asleep in an unstimulating environment, measured latency (in minutes) to sleep onset averaged over 4 test sessions at 2-hour intervals. For each test session, the subject was told to lie quietly and attempt to sleep. Each test session was terminated after 20 minutes if no sleep occurred or immediately after sleep onset.

The primary measures of effectiveness were: 1) sleep latency as assessed by the Maintenance of Wakefulness Test (MWT) and 2) the change in the patient's overall disease status, as measured by the CGI-C at the final visit. Each MWT test session was terminated after 20 minutes if no sleep occurred or immediately after onset in this study.

Patients treated with NUVIGIL showed a statistically significantly enhanced ability to remain awake on the MWT at each dose compared to placebo at final visit (See Table 4). A statistically significant greater number of patients treated with NUVIGIL at each dose showed improvement in overall clinical condition as rated by the CGI-C scale at final visit (Table 5).

The two doses of NUVIGIL produced statistically significant effects of similar magnitudes on the CGI-C. Although a statistically significant effect on the MWT was observed for each dose, the magnitude of effect was observed to be greater for the higher dose.

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

Table 4: Average Baseline Sleep Latency and change from baseline at final visit (MWT and MSLT in minutes):

Disorder	**Measure**	**NUVIGIL 150 mg[a]**		**NUVIGIL 250 mg[a]**		**Placebo**	
		Base-line	*Change from Base-line*	*Base-line*	*Change from Baseline*	*Base-line*	*Change from Baseline*
Narcolepsy	MWT	12,1	1,3	9,5	2,6	12,5	-1,9

[a] Significantly different than placebo for all trials (p< 0,05)

Table 5: Clinical Global Impression of Change (CGI-C) (Percentage of patients who improved at final visit):

Disorder	**NUVIGIL 150 mg[a]**	**NUVIGIL 250 mg[a]**	**Placebo**
Narcolepsy	69 %	73 %	33 %

[a] Significantly different than placebo for all trials (p< 0,05)

5.2 Pharmacokinetic properties:

Armodafinil exhibits linear time-independent kinetics following single and multiple oral dose administration. Increase in systemic exposure is proportional over the dose range of 50 to 400 mg. No time-dependent change in kinetics was observed through 12 weeks of dosing. Apparent steady state for armodafinil was reached within 7 days of dosing. At steady state, the systemic exposure for armodafinil is 1,8 times the exposure observed after a single dose. The concentration-time profiles of the (R)-enantiomer following administration of a single-dose of 50 mg NUVIGIL or 100 mg modafinil [a 1:1 mixture of (R)- and (S)-enantiomers] are nearly superimposable. However, the C_{max} and $AUC_{0-\infty}$, of armodafinil at steady-state were approximately 37 % and 70 % higher, respectively, following administration of 200 mg NUVIGIL than the corresponding values of modafinil following administration of 200 mg modafinil due to the more rapid clearance of the (S)-enantiomer (elimination half-life approximately 4 hours) as compared to the (R)-enantiomer.

Absorption:

NUVIGIL is readily absorbed after oral administration. The absolute oral bioavailability was not determined due to the aqueous insolubility of armodafinil, which precluded intravenous administration. Peak plasma concentrations are attained at approximately 2 hours in the fasted state.

Effect of Food:

Food effect on oral bioavailability of NUVIGIL is considered minimal; however, time to reach peak concentration (T_{max}) may be delayed by approximately 2-4 hours in the fed state. Since the delay in T_{max} is also associated with elevated plasma concentrations later in time, food can potentially effect the onset and time course of the pharmacologic action for NUVIGIL.

Distribution:

NUVIGIL has an apparent volume of distribution of approximately 42 L. Data specific to armodafinil protein binding are not available. The potential for interactions of NUVIGIL with highly protein-

bound medicines is considered to be minimal.

Biotransformation:

In vitro and *in vivo* data show that armodafinil undergoes hydrolytic deamidation, S-oxidation, and aromatic ring hydroxylation, with subsequent glucuronide conjugation of the hydroxylated products. Amide hydrolysis is the single most prominent metabolic pathway, with sulfone formation by cytochrome P450 (CYP) 3A4/5 being next in importance. The other oxidative products are formed too slowly *in vitro* to enable identification of the enzyme(s) responsible. Only two metabolites reach appreciable concentrations in plasma [i.e., (R)-modafinil acid and modafinil sulfone].

Data specific to NUVIGIL disposition are not available. However, modafinil is mainly eliminated via metabolism, predominantly in the liver, with less than 10 % of the parent compound excreted in the urine. A total of 81 % of the administered radioactivity was recovered in 11 days post-dose, predominantly in the urine (80 % vs. 1,0 % in the faeces).

Elimination:

After oral administration of NUVIGIL, armodafinil exhibits an apparent monoexponential decline from the peak plasma concentration. The apparent terminal t½ is approximately 15 hours. The oral clearance of NUVIGIL is approximately 33 ml/min.

Special populations:

Children:

The pharmacokinetics of armodafinil have not been studied in children.

Age:

In a clinical study, systemic exposure of armodafinil was approximately 15 % higher in elderly

subjects (≥ 65 years of age, N=24), corresponding to approximately 12 % lower oral clearance (CL/F), as compared to young subjects (18-45 years of age, N=25). Systemic exposure of armodafinil acid (metabolite) was approximately 61 % and 73 % greater for C_{max} and $AUC_{0-\tau}$, respectively, compared to young subjects. Systemic exposure of the sulfone metabolite was approximately 20 % lower for elderly subjects compared with young subjects. A subgroup analysis of elderly subjects demonstrated elderly subjects ≥75 and 65-74 years of age had approximately 21 % and 9 % lower oral clearance, respectively, compared to young subjects. Systemic exposure was approximately 10 % greater in subjects 65-74 years of age (N=17) and 27 % greater in subjects ≥75 years of age (N=7), respectively, when compared to young subjects. The change is considered not likely to be clinically significant for elderly patients, however, because some elderly patients have greater exposure to armodafinil, consideration should be given to the use of lower doses.

Gender:

Population pharmacokinetic analysis suggests no gender effect on the pharmacokinetics of armodafinil.

Race:

The influence of race on the pharmacokinetics of armodafinil has not been studied.

Renal impairment:

In a single dose 200 mg modafinil study, severe chronic renal failure (creatinine clearance ≤20 ml/min) did not significantly influence the pharmacokinetics of modafinil, but exposure to modafinil acid (metabolite) was increased 9 fold. There is inadequate information to determine safety and efficacy of NUVIGIL (armodafinil) dosing in patients with renal impairment, mild, moderate or severe.

Hepatic impairment:

The pharmacokinetics and metabolism of modafinil were examined in 6 men and 3 women with liver cirrhosis. Three patients had stage B or B+ cirrhosis and 6 patients had stage C or C+ cirrhosis (per the Child-Pugh score criteria). Clinically 8 of 9 patients were icteric and all had ascites. In these patients, the oral clearance of modafinil was decreased by about 60 % and the steady state concentration was doubled compared to normal patients.

Therefore, the dose of NUVIGIL should be reduced by half in patients with moderate and severe hepatic impairment (see **sections 4.2** and **4.4**). There is a lack of data on dosing information for NUVIGIL (armodafinil) specific to the degree of liver impairment.

5.3 Preclinical safety data:

Genotoxicity:

Armodafinil was negative in genotoxicity *in vitro* tests.

Carcinogenicity:

The exposure of armodafinil in 2-year carcinogenicity studies in mice and rats was insufficient to adequately assess carcinogenic potential.

Reproductive toxicity:

Oral administration of armodafinil to pregnant rats and rabbits throughout organogenesis resulted in increased incidences of foetal structural alterations and foetal toxicity at the highest dose. The highest no-effect dose for embryo foetal developmental toxicity was associated with a plasma armodafinil exposure (AUC) less than that in humans at the maximum recommended human dose (MRHD) of NUVIGIL (250 mg/day) (see **section 4.6**).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Croscarmellose Sodium

Lactose Monohydrate

Magnesium Stearate

Microcrystalline Cellulose

Povidone K29/32

Pregelatinised Starch

6.2 Incompatibilities:

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life:

5 years.

6.4 Special precautions for storage:

Store at or below 25 °C.

Protect from light and moisture.

Keep the blisters in the outer container until required for use.

6.5 Nature and contents of container:

NUVIGIL tablets are available in either:

White square HDPE bottles with white child-resistant closures and an induction-sealed liner.

Clear PVC and silver aluminium blisters strips packed into outer cardboard cartons.

The available pack sizes are blister packs of 7 or 30 tablets, and HDPE bottles of 30 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

Any unused medicine or waste material should be disposed of by taking to your local

pharmacy.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

TEVA PHARMACEUTICALS (PTY) LTD,

Maxwell Office Park,

Magwa Crescent West,

Waterfall City,

Midrand,

Gauteng,

2090

8. REGISTRATION NUMBER(S):

NUVIGIL 50 mg: 48/1.1/1129

NUVIGIL 150 mg: 48/1.1/1130

NUVIGIL 250 mg: 48/1.1/1131

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

20 April 2021

10. DATE OF REVISION OF THE TEXT:

15 November 2024