New drugs

Armodafinil

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Approved indication: sleep disorders

Nuvigil (Teva Pharmaceuticals)
50 mg, 150 mg and 250 mg tablets
Australian Medicines Handbook Appendix A

Armodafinil is a psychostimulant that aims to improve wakefulness. It is indicated for narcolepsy, obstructive sleep apnoea or hypopnea syndrome (added to continuous positive airways pressure) and for chronic shift work sleep disorder when non-drug approaches have not worked.

Armodafinil is related to modafinil, which is already registered in Australia for the same indications.[1] Modafinil is a 1:1 mixture of R and S isomers whereas armodafinil consists only of the R isomer. Like modafinil, armodafinil's exact mechanism of action is unknown.

The absorption, metabolism and elimination of armodafinil are very similar to modafinil. However, after oral administration peak serum concentrations and exposure (area under the curve) are higher for armodafinil than for modafinil at the same dose. Armodafinil is not therefore bioequivalent to modafinil and cannot be directly substituted.

Armodafinil should be taken once a day in the morning for narcolepsy and obstructive sleep apnoea, and one hour before starting work for those with shift work sleep disorder. As with modafinil, the armodafinil dose should be reduced in people with severe hepatic impairment. Lower doses should also be considered in older people due to reduced clearance of the drug.

Armodafinil (150 mg or 250 mg) has been assessed in several 12-week placebo-controlled trials (see Table).[2-5] In daytime maintenance of wakefulness tests, patients with narcolepsy or obstructive sleep apnoea stayed awake up to 4.5 minutes longer with armodafinil than with placebo.[2-4] In night-time multiple sleep latency tests, patients with excessive sleepiness due to shift work disorder stayed awake on average 2.7 minutes longer with armodafinil than with placebo.[5]

The most common adverse events with armodafinil were headache, nausea, dizziness and insomnia. In the trials, 7% of people discontinued the drug because of an adverse event. Headache was the most common reason, but others included psychiatric symptoms such as anxiety, agitation, irritability and depression. There have been cases of suicide in patients taking armodafinil.

In a 12-month open-label trial in 328 patients with narcolepsy, obstructive sleep apnoea or shift work disorder, rare but serious adverse events that were possibly related to armodafinil included chest pain, pulmonary embolism, myocardial infarction and exacerbation of depression.[6]

Rashes have been reported with armodafinil, including a fatal case of Stevens-Johnson syndrome. The drug should be stopped immediately if a rash develops.

The potential drug interactions with armodafinil are expected to be similar to modafinil. Armodafinil weakly induces cytochrome P450 (CYP) 3A4 so may

Table **Efficacy of armodafinil in sleep disorders**

Disorder	Trial (patients treated)	Mean change in minutes of wakefulness from baseline*		
		Armodafinil 150 mg	Armodafinil 250 mg	Placebo
Narcolepsy	Harsh et al. (196 patients)[2]	+1.3 (baseline=12.1)	+2.6 (baseline=9.5)	-1.9 (baseline=12.5)
Obstructive sleep apnoea or hypopnea syndrome	Hirschkowitz et al. (259 patients)[3]	+2.3 (baseline=23.7)	–	-1.3 (baseline=23.3)
	Roth et al. (392 patients)[4]	+1.7 (baseline=21.5)	+2.2 (baseline=23.3)	-1.7 (baseline=23.2)

* The ability to stay awake during the day was measured in maintenance of wakefulness tests using polysomnography at baseline and after 12 weeks of treatment. Results are a mean of four tests conducted at 2-hour intervals.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

reduce concentrations of drugs that are metabolised by this enzyme such as hormonal contraceptives, cyclosporin, carbamazepine and midazolam. Armodafinil also inhibits CYP2C19 and may increase concentrations of CYP2C19 substrates such as omeprazole, phenytoin, diazepam, propranolol and clomipramine. More frequent monitoring of INR may be required with co-administered warfarin.

Because of its interaction with hormone contraceptives, women taking armodafinil should use alternative contraception. Armodafinil is contraindicated in pregnancy and not recommended during lactation based on previous animal studies with modafinil showing fetal effects and excretion in breast milk.

Armodafinil significantly improved the ability of patients to stay awake for longer than a placebo. However, this was only by a matter of minutes in sleep latency tests. Although rare, fatalities relating to armodafinil, including from serious skin reactions, have occurred. Psychiatric symptoms can also be a problem. As armodafinil may produce euphoric effects, prescribers should be aware of its potential for abuse.

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The Transparency Score (T) is explained in 'New drugs: transparency', Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration (www.fda.gov) and the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-austpar.htm).