

## Volinanserin (MDL-100,907 / M100907)

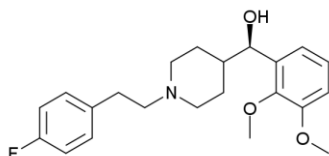
**Volinanserin (MDL-100,907)** is a highly selective 5-HT<sub>2A</sub> receptor antagonist. It is widely used in scientific research to investigate the function of the 5-HT<sub>2A</sub> receptor. Volinanserin is also being trialed as a potential antipsychotic, antidepressant and treatment for insomnia.

M-100907 is a highly selective 5-HT<sub>2A</sub> antagonist that is being developed by Aventis Pharmaceuticals, formerly Hoechst Marion Roussel (HMR), for the potential treatment of schizophrenia. M-100907 was in phase III trials for chronic schizophrenia. In August 1999, development was discontinued for acute schizophrenia (schizoaffective disorder) on the basis of poor results. M-100907 is also active in animal models involving blockade of NMDA glutamatergic channel receptors, an effect known to resemble some behavioral symptoms of schizophrenia in man. M-100907 is also claimed in other patents for the treatment of thromboembolic disorders, for the treatment of various developmental neurological disorders such as autism and attention deficit hyperactivity disorder.

[Ref: de Paulis T. M-100907 (Aventis). *Curr Opin Investig Drugs*. 2001 Jan;2(1):123-32. PubMed PMID: 11527004.]

**Chemical Name:** (R)-(+)- $\alpha$ -(2,3-Dimethoxyphenyl)-1-[2-(4-fluorophenyl)ethyl]-4-piperidinemethanol

**Formula:** C<sub>22</sub>H<sub>28</sub>FNO<sub>3</sub>



**Molecular Mass:** 373.46 g/mol

**Availability:** M100907 ; formerly MDL 100,907

Sanofi-Aventis

Axon: Cat. No. Axon 1104 Ordering Information: [order@axonmedchem.com](mailto:order@axonmedchem.com)

### Receptor Affinity

<p>Sub-nanomolar affinity (K<sub>d</sub> = 0.14-0.19 nM in human brain; K<sub>d</sub> = 0.16-0.19 nM in monkey brain) and presented a pharmacological profile consistent with its binding to 5-HT<sub>2A</sub> receptors</p> <p>Rank order of affinity for [<sup>3</sup>H]MDL 100,907-labeled receptors: MDL 100,907 &gt; spiperone &gt; ketanserin &gt; mesulergine. The data obtained after quantifying the autoradiograms in layer III of frontal cortex and occipital cortex in human brain, and in insular cortex (layer III) and claustrum of monkey brain.</p> <p>Studies from monkey brains revealed a somatodendritic localization of these receptors.</p>	<p>López-Giménez JF, Vilaró MT, Palacios JM, Mengod G. [<sup>3</sup>H]MDL 100,907 labels 5-HT<sub>2A</sub> serotonin receptors selectively in primate brain. <i>Neuropharmacology</i>. 1998 Sep;37(9):1147-58. PubMed PMID: 9833645.</p>
<p><i>In vivo</i> binding time course studies demonstrated that [<sup>3</sup>H]M100907 exhibits low non-specific binding in the cerebellum, while sustaining high levels of specific binding in the rat frontal cortex through 120 min post administration. These data are consistent with previous studies which have used this radioligand for receptor occupancy measurements in rat and human brain.</p>	<p>Ito et al., 1998 H. Ito, S. Nyberg, C. Halldin, C. Lundkvist and L. Farde, PET imaging of central 5-HT<sub>2A</sub> receptors with carbon-11-MDL 100,907. <i>J Nucl Med</i>, 39 (1998), pp. 208-214.</p> <p>Lopez-Gimenez et al., 1997 J.F. Lopez-Gimenez, G. Mengod, J.M. Palacios and M.T. Vilaro, Selective visualization of rat brain 5-HT<sub>2A</sub></p>

	receptors by autoradiography with [ <sup>3</sup> H]MDL 100,907. <i>Naunyn Schmiedebergs Arch. Pharmacol.</i> , 356 (1997), pp. 446–454.
In human <i>in vivo</i> PET studies, the highest radioactivity concentration was observed in the neocortex, whereas radioactivity was lower in the cerebellum, pons, thalamus, striatum and white matter. The binding potential in the neocortical regions was 4-6 times higher, whereas binding potential in the striatum was slightly higher than that in the cerebellum, demonstrating a regional distribution in good agreement with 5-HT <sub>2A</sub> receptor densities measured <i>in vitro</i> . The binding potential in the cerebellum was small but not negligible. Thus, [ <sup>11</sup> C]MDL 100,907 is recommended in the future for PET studies in healthy subjects and schizophrenic patients, including the determination of drug-induced 5-HT <sub>2A</sub> receptor occupancy.	Ito et al., 1998 H. Ito, S. Nyberg, C. Halldin, C. Lundkvist and L. Farde, PET imaging of central 5-HT <sub>2A</sub> receptors with carbon-11-MDL 100,907. <i>J Nucl Med</i> , 39 (1998), pp. 208–214.
<b>Time course of [<sup>3</sup>H]M100907 binding in rat frontal cortex and cerebellum</b>  Using 7.5 µCi/rat, radioactivity measurements (DPMs) were obtained in the frontal cortex and cerebellum at various times following intravenous [ <sup>3</sup> H]M100907 administration. Radioligand binding steadily increased in the frontal cortex from 1957 ± 62.4 (mean ± S.E.M.) DPMs at 1 min, to a maximal level of 3525 ± 94.5 DPMs at 30 min. Frontal cortex binding remained high (> 3000 DPMs) across the remaining time intervals of 60, 90, and 120 min. By contrast, maximal cerebellum binding of 1113 ± 43.7 DPMs was exhibited at 1 min, with a gradual time-dependent decrease to 453 ± 45.2 DPMs at 120 min. The largest specific binding windows were observed from 30–120 min	Knauer CS, Campbell JE, Galvan B, Bowman C, Osgood S, Buist S, Buchholz L, Henry B, Wong EH, Shahid M, Grimwood S. Validation of a rat <i>in vivo</i> [(3)H]M100907 binding assay to determine a translatable measure of 5-HT(2A) receptor occupancy. <i>Eur J Pharmacol.</i> 2008 Sep 4;591(1-3):136-41. Epub 2008 Jun 19. PubMed PMID:18593577.

## Receptor Occupancy

Patients dosed with 20 mg of M100907 had a mean plasma concentration of 14.5 ± 8.6 ng/ml, with a corresponding 5-HT <sub>2A</sub> receptor occupancy of 87 ± 7% using PET imaging.	G. Grunder, F. Yokoi, S.J. Offord, H.T. Ravert, R.F. Dannals, J.K. Salzmman, S. Szymanski, P.D. Wilson, D.R. Howard and D.F. Wong, Time course of 5-HT <sub>2A</sub> receptor occupancy in the human brain after a single oral dose of the putative antipsychotic drug MDL 100,907 measured by positron emission tomography. <i>Neuropsychopharmacology</i> , 17 (1997), pp. 175–185.  Offord SJ, Wong DF, Nyberg S. The role of positron emission tomography in the drug development of M100907, a putative antipsychotic with a novel mechanism of action. <i>J Clin Pharmacol.</i> 1999 Aug;Suppl:17S-24S. Review. PubMed PMID: 10434243.
The 5-HT <sub>2A</sub> receptor occupancy was determined in two	Talvik-Lotfi M, Nyberg S, Nordström AL, Ito

patients with schizophrenia treated with M100907, 20 mg once a day. Positron emission tomography (PET) with (11)C-labeled M100907, was performed pre-study and under steady state conditions. M100907 was well tolerated and induced a very high 5-HT <sub>2A</sub> receptor occupancy in the frontal cortex of both patients (>90%).	H, Halldin C, Brunner F, Farde L. High 5HT <sub>2A</sub> receptor occupancy in M100907-treated schizophrenic patients. <i>Psychopharmacology (Berl)</i> . 2000 Mar;148(4):400-3. PubMed PMID: 10928313.
Consistent with previous human studies, M100907 demonstrated dose-dependent increases in 5-HT <sub>2A</sub> receptor occupancy with an ED <sub>50</sub> of 0.100 mg/kg at 60 min. Of particular importance, M100907 exhibited 92.8 ± 2.84% receptor occupancy when the average plasma concentration was 18.8 ± 7.06 ng/ml. The similarities shown between the rat and human data provide confidence that rat <i>in vivo</i> binding measures of receptor occupancy are translatable to human PET imaging studies.	Knauer CS, Campbell JE, Galvan B, Bowman C, Osgood S, Buist S, Buchholz L, Henry B, Wong EH, Shahid M, Grimwood S. Validation of a rat <i>in vivo</i> [(3)H]M100907 binding assay to determine a translatable measure of 5-HT(2A) receptor occupancy. <i>Eur J Pharmacol</i> . 2008 Sep 4;591(1-3):136-41. Epub 2008 Jun 19. PubMed PMID:18593577.

### Antidepressant

5-HT<sub>2A</sub> receptors might enhance the therapeutic effectiveness of SSRIs.

<p>M100907 and low doses of a SSRI using a behavioral screen in rodents (the differential-reinforcement-of low rate 72-s schedule of reinforcement; DRL 72-s) which previously has been shown to be sensitive both to 5-HT<sub>2</sub> antagonists and SSRIs. M100907 has a ~ 100-fold or greater selectivity at 5-HT<sub>2A</sub> receptors vs other 5-HT receptor subtypes, and would not be expected to appreciably occupy non-5-HT<sub>2A</sub> receptors at doses below 100 µg/kg.</p> <p>The apparent synergistic effects of M100907 and fluoxetine on rats performing on the DRL 72-s schedule argue for a pharmacodynamic rather than a pharmacokinetic mechanism underlying this behavioral drug-drug interaction. This represents the first preclinical report suggesting that selective blockade of 5-HT<sub>2A</sub> receptors may have a synergistic effect with blockade of serotonin transporters.</p> <p>The combined blockade of 5-HT<sub>2A</sub> receptors and serotonin transporters may result in greater efficacy in treating neuropsychiatric syndromes than blocking either site alone.</p>	<p>Ref Marek GJ, Martin-Ruiz R, Abo A, Artigas F (December 2005). "The selective 5-HT<sub>2A</sub> receptor antagonist M100907 enhances antidepressant-like behavioral effects of the SSRI fluoxetine". <i>Neuropsychopharmacology</i> 30 (12): 2205–15.</p>
<p><b>Future Studies</b></p> <p>Testing the combination of a highly selective 5-HT<sub>2A</sub> receptor antagonist like M100907 together with an SSRI or a new chemical entity with selective blockade of both 5-HT<sub>2A</sub> and serotonin transporter in the same molecule would be a critical clinical experiment to test this hypothesis.</p> <p>A second implication open for future studies is whether selective blockade of 5-HT<sub>2A</sub> receptors can also have an additive or synergistic action in the treatment of other diverse neuropsychiatric syndromes for which SSRIs are a useful therapeutic modality</p>	

## Antipsychotic

M100907 is predicted to be effective for both positive and negative symptoms of schizophrenia without the liability of extrapyramidal side effects.

MDL 100,907 blocked the slowing of ventral tegmental area (A10) dopaminergic neurons by amphetamine but, like clozapine, produced only small increases in the number of active substantia nigra zona compacta (A9) and A10 dopamine neurons after acute administration in mice. When administered chronically, MDL 100,907 and clozapine selectively reduced the number of spontaneously active A10 neurons, whereas haloperidol reduced activity in both the A9 and A10 regions.	Sorensen SM, Kehne JH, Fadayer GM, Humphreys TM, Ketteler HJ, Sullivan CK, Taylor VL, Schmidt CJ. Characterization of the 5-HT <sub>2</sub> receptor antagonist MDL 100907 as a putative atypical antipsychotic: behavioral, electrophysiological and neurochemical studies. <i>J Pharmacol Exp Ther</i> . 1993 Aug;266(2):684-91. PubMed PMID:8102646.
MDL 100,907, with chronic treatment, produced a significant decrease in the number of active ventral tegmental (A10) dopamine neurons while inhibiting the substantia nigra (A9) dopamine neurons to a much lesser extent .	Palfreyman MG, Schmidt CJ, Sorensen SM, Dudley MW, Kehne JH, Moser P, Gittos MW, Carr AA. Electrophysiological, biochemical and behavioral evidence for 5-HT <sub>2</sub> and 5-HT <sub>3</sub> mediated control of dopaminergic function. <i>Psychopharmacology (Berl)</i> . 1993;112(1 Suppl):S60-7. PubMed PMID: 7831442.
M100,907 was infused directly into the mPFC of conscious rats. This resulted in a concentration-dependent blockade of K(+)-stimulated DA release.	E.A. Pehec, H.G. McFarlane, K. Maguschak, B. Price and C.P. Pluto, M100,907, a selective 5-HT(2A) antagonist attenuates dopamine release in the rat medial prefrontal cortex. <i>Brain Res</i> , 888 (2001), pp. 51–59.
Similar to clozapine, M100907 increased dopamine release in the prefrontal cortex of rats, region associated with negative symptoms.	Schmidt CJ, Fadayer GM: The selective 5-HT <sub>2</sub> receptor antagonist, MDL 100,907, increases dopamine efflux in the prefrontal cortex of the rat. <i>Eur J Pharmacol</i> 1995;273:273-279.
Intrastriatal infusions of MDL 100,907 via the microdialysis probe directly into the brains of awake, freely moving rats produced a concentration-dependent inhibition of MDMA-induced dopamine release.	Schmidt CJ, Sullivan CK, Fadayer GM. Blockade of striatal 5-hydroxytryptamine <sub>2</sub> receptors reduces the increase in extracellular concentrations of dopamine produced by the amphetamine analogue 3,4-methylenedioxymethamphetamine. <i>J Neurochem</i> . 1994 Apr;62(4):1382-9. PubMed PMID: 7907650.
Acute intravenous administration of M100907 (0.03 and 0.3 mg/kg), selectively increased dopamine output in the shell of the nucleus accumbens.	Marcus MM, Nomikos GG, Svensson TH. Effects of atypical antipsychotic drugs on dopamine output in the shell and core of the nucleus accumbens: role of 5-HT(2A) and alpha(1)-adrenoceptor antagonism. <i>Eur Neuropsychopharmacol</i> . 2000 Jul;10(4):245-53. PubMed PMID: 10871706.

## Insomnia

<p>5-HT<sub>2A</sub> receptor knock-out mice show a significant increase of wakefulness and a reduction of slow wave sleep while REM sleep remains unchanged. Systemic injection of MDL 100907 significantly increased slow wave sleep and reduced wakefulness and REM sleep.</p> <p>MDL 100907 (at 2–5 mg/kg, i.p.), induced a significant dose-dependent increase in non-REM sleep amounts during the first 3 h after injection in 5-HT<sub>2A</sub><sup>+/+</sup> mice. The drug also caused a decrease in wakefulness and REM sleep amounts during the same period. As expected, no effect of MDL 100907 was observed on the states of vigilance in 5-HT<sub>2A</sub><sup>-/-</sup> animals.</p>	<p>Popa D, Léna C, Fabre V, Prenat C, Gingrich J, Escourrou P, Hamon M, Adrien J. Contribution of 5-HT<sub>2</sub> receptor subtypes to sleep-wakefulness and respiratory control, and functional adaptations in knock-out mice lacking 5-HT<sub>2A</sub> receptors. J Neurosci. 2005 Dec 7;25(49):11231-8. PubMed PMID: 16339018.</p>
<p>Mice underwent sleep deprivation and/or a blockade of opioidergic receptors with naloxone. The action of the "sleep deprivation-opioid understimulation" combination is antagonized completely by pretreatment of MDL 100,907.</p>	<p>Ionov ID. Synergistic effect of decreased opioid activity and sleep deprivation on head-twitch response in mice. Pharmacol Biochem Behav. 2010 Jul;96(1):48-51. Epub 2010 Apr 14. PubMed PMID: 20399224.</p>
<p>MDL100907 (0.1, 1.0 and 3.0 mg/kg ip) produced significant increases in sleep and decreases in waking in Wistar rats, compared with vehicle control. All 3 doses of MDL produced more consolidated sleep, increased non-rapid eye movement sleep (NREM) sleep, and increased electroencephalographic delta power during NREM sleep. MDL 100907 did not affect rapid eye movement sleep though it reduced body temperature relative to vehicle-injected controls.</p>	<p>Morairty SR, Hedley L, Flores J, Martin R, Kilduff TS. Selective 5HT<sub>2A</sub> and 5HT<sub>6</sub> receptor antagonists promote sleep in rats. Sleep. 2008 Jan;31(1):34-44. PubMed PMID: 18220076; PubMed Central PMCID: PMC2225549.</p>
<p><b>Efficacy and Safety of Volinanserin on Sleep Maintenance Insomnia - Polysomnographic Study (NOCTURNE907)</b></p> <p>The purpose of this Phase III study is to assess efficacy and safety of volinanserin (M100907) in the population of patients complaining of sleep maintenance insomnia. The patients suffering from that condition frequently wake up during the night, their sleep is non restorative and they suffer from a significant distress or impairment in their daily activities consecutive to insomnia.</p> <p><b>Official Title:</b> Efficacy and Safety of 2 mg/Day M100907 on Sleep Maintenance Insomnia: a 6-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Polysomnographic study</p> <p><b>Sponsor:</b> Sanofi-Aventis</p> <p><b>Status:</b> Completed</p> <p><b>Results:</b> No study results posted</p> <p><b>Further study details as provided by Sanofi-Aventis:</b></p> <p>Change from baseline to 6 weeks of treatment of the mean night polysomnographic (NPSG) wake time after sleep onset (WASO). [ Time Frame: 6 weeks; start date: April 2007 ]</p> <p>Comparison of Volinanserin and Lormetazepam in the Treatment of Insomnia Characterized by Sleep Maintenance Difficulties (REST) - This study has been terminated.</p>	