

RESEARCH MONOGRAPH . COMPOUND PROFILE

Adrafinil

A benzhydryl sulfinyl hydroxamic acid developed at Laboratoire Lafon as a vigilance-promoting agent for elderly patients, distinguished from classical psychostimulants by its prodrug relationship to modafinil and by a wakefulness mechanism mediated principally through atypical dopamine transporter inhibition and downstream orexinergic, histaminergic, and glutamatergic activation.

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ABSTRACT

Adrafinil (CRL-40028, Olmifon) is a synthetic diphenylmethyl sulfinyl hydroxamic acid compound and the first clinically introduced member of the eugeroic (wakefulness-promoting) pharmacological class, marketed in France from 1986 to 2011 for the treatment of inattention, drowsiness, and vigilance deficits in elderly patients. The compound functions as a prodrug: hepatic metabolism converts adrafinil to its primary active metabolite modafinil (CRL-40476, 2-diphenylmethylsulfinylacetamide), which was subsequently developed independently and received regulatory approval in the United States (1998), the European Union, and more than 20 additional jurisdictions for the treatment of narcolepsy, obstructive sleep apnea-associated excessive daytime sleepiness, and shift work sleep disorder. The prodrug conversion proceeds through enzymatic hydrolysis of the terminal hydroxamic acid to yield modafinil, with concurrent production of the inactive metabolite modafinilic acid (CRL-40467). The pharmacological activity of adrafinil is therefore substantially attributable to modafinil, an atypical dopamine reuptake inhibitor that binds the dopamine transporter (DAT) with low micromolar affinity (K_i approximately 2.3 micromolar) and produces wake-promoting effects through a cascade involving elevated extracellular dopamine, activation of D1 and D2 dopamine receptors, downstream stimulation of lateral hypothalamic orexin (hypocretin) neurons, secondary activation of tuberomammillary histaminergic projections, and modulation of cortical glutamatergic and GABAergic tone. Positron emission tomography studies in humans have demonstrated that modafinil at clinical doses occupies approximately 50 to 57 percent of

striatal dopamine transporters, an occupancy level comparable to methylphenidate, though modafinil produces substantially less reinforcing subjective effects and lower abuse liability than classical psychostimulants. Clinical evidence for adrafinil itself is confined to six principal studies conducted in France between 1979 and the mid-1990s, predominantly in ambulatory and hospitalized elderly patients (aged 45 years and older, majority older than 65 years) exhibiting vigilance, attention, memory, and affective complaints. These studies reported improvements in attention, wakefulness, self-evaluated vigilance, depressive symptom scores, and functional autonomy, though the trial designs, outcome measures, and sample sizes did not meet the evidentiary standards that would later govern modafinil registration. The compound was voluntarily withdrawn from the French market in September 2011 following a regulatory review by the Commission d'Autorisation de Mise sur le Marche that concluded the clinical evidence was insufficient to establish benefit and that the known adverse effect profile, including hepatic enzyme elevations with chronic use and rare skin reactions, constituted an unfavorable risk-benefit ratio given the availability of modafinil as a more potent, better characterized, and directly acting alternative. Adrafinil is not a controlled substance in the United States, the United Kingdom, Canada, or most other jurisdictions, and is sold as an unregulated research compound and dietary supplement. This monograph reviews the chemistry, synthesis, and stereochemistry of adrafinil; the prodrug conversion and the molecular pharmacology of its active metabolite modafinil; the pharmacokinetic profile including hepatic biotransformation; the preclinical pharmacology in rodent, feline, and primate models; the clinical evidence base across vigilance, narcolepsy, and cognitive endpoints; sourcing

and quality verification considerations; reconstitution and handling; stack-interaction implications; adverse-event signal including hepatotoxicity; and a structured comparative assessment of five wakefulness-promoting alternatives against adrafinil on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Adrafinil.

Marketed name: Olmifon (Laboratoire Lafon, later Cephalon; France, 1986 to 2011). The compound was marketed exclusively in France and was not registered in other major pharmaceutical markets.

Development code: CRL-40028 (Laboratoire Lafon). The development code is the canonical identifier in the early pharmacology literature and appears in all seminal publications from the Lafon research group and from the Jouvett laboratory in Lyon [1, 2].

Chemical Abstracts Service registry number: 63547-13-7.

International Union of Pure and Applied Chemistry name: 2-(diphenylmethylsulfinyl)-N-hydroxyacetamide. The compound is alternatively described as 2-(benzhydrylsulfinyl)acetohydroxamic acid. The systematic name reflects the three principal structural features: the diphenylmethyl (benzhydryl) group, the sulfinyl (sulfoxide) linker, and the terminal hydroxamic acid (N-hydroxyacetamide) moiety.

1.2 Structural class and chemistry

Adrafinil is a member of the benzhydryl sulfinyl class of synthetic wakefulness-promoting agents (eugeroics). The structural class was originated at Laboratoire Lafon in Maisons-Alfort, France, during a screening program for analgesic compounds in the early 1970s and subsequently gave rise to modafinil (CRL-40476, the des-hydroxy acetamide) and armodafinil (the R-enantiomer of modafinil) [3, 4].

Molecular formula: C₁₅H₁₅NO₃S.

Exact mass: 289.0773 g/mol (monoisotopic).

Molecular weight: 289.35 g/mol.

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide, sparingly soluble in methanol and ethanol, poorly soluble in water. Melting point is approximately 159 to 160 degrees Celsius. The compound is stable under standard storage conditions at room temperature in dry form.

Stereochemistry: Adrafinil contains one stereocenter at the sulfinyl sulfur atom, giving rise to (R)- and (S)-enantiomers. The marketed material (Olmifon) and the commercially available research-grade compound are racemic mixtures. The individual enantiomers have not been separately characterized in clinical studies of adrafinil itself, though the stereochemistry of the active metabolite modafinil has been extensively studied: the R-enantiomer of modafinil (armodafinil) has a longer elimination half-life and higher sustained plasma concentrations than the S-enantiomer, and armodafinil has been independently developed and marketed (Nuvigil, Cephalon/Teva) [5]. The stereochemical implications for adrafinil metabolism (whether enantioselective conversion to modafinil occurs) have not been definitively characterized.

Relationship to modafinil: Adrafinil differs from modafinil by a single structural modification: the terminal amide nitrogen of modafinil (CONH₂) bears a hydroxyl group in adrafinil (CON(OH)H), making adrafinil a hydroxamic acid and modafinil a simple amide. The hydroxamic acid is cleaved in vivo by hepatic enzymes to yield modafinil. This structural relationship establishes adrafinil as a prodrug of modafinil [6].

1.3 Synthesis

The published synthesis of adrafinil proceeds in four principal stages [7, 8]:

Stage 1, formation of benzhydryl thioacetic acid: Benzhydrol (diphenylmethanol) is reacted with thioglycolic acid in the presence of an acid catalyst (trifluoroacetic acid or boron trifluoride etherate) under reflux conditions to produce 2-(benzhydrylthio)acetic acid through a nucleophilic substitution at the benzylic carbon.

Stage 2, conversion to the hydroxamic acid intermediate: The carboxylic acid is activated as the acid chloride using thionyl chloride, then reacted with hydroxylamine (typically as the hydrochloride salt in the presence of base, or as a free base solution) to form 2-(benzhydrylthio)acetohydroxamic acid, the thioether precursor of adrafinil.

Stage 3, oxidation to the sulfinyl (sulfoxide): The thioether intermediate is dissolved in glacial acetic acid, and a controlled stoichiometric quantity of hydrogen peroxide (30 percent aqueous) is added dropwise at approximately 40 to 45 degrees Celsius. The reaction is monitored to prevent over-oxidation to the sulfone. The product is the racemic sulfoxide, adrafinil.

Stage 4, purification: The crude product is extracted into ethyl acetate, washed, dried, and recrystallized from ethyl acetate/isopropanol (approximately 3:2) to yield analytically pure adrafinil as a white crystalline solid. Typical yields for the oxidation step are 70 to 85 percent. The product is characterized by nuclear magnetic resonance spectroscopy, infrared spectroscopy, high-performance liquid chromatography, and melting point determination.

The synthesis of modafinil follows a parallel route but substitutes ammonia or ammonium hydroxide for hydroxylamine in Stage 2, yielding the simple acetamide rather than the hydroxamic acid. The industrial syntheses of both compounds have been extensively optimized by Lafon, Cephalon, and generic manufacturers.

2. Abstract

Adrafinil (CRL-40028, Olmifon) is a synthetic eugeroic compound of the benzhydryl sulfinyl class that functions as a prodrug of modafinil (CRL-40476), the prototypical atypical wakefulness-promoting agent [1, 3]. Discovered in 1974 at Laboratoire Lafon in Maisons-Alfort, France, during a screening program for analgesic compounds, adrafinil was the first member of the eugeroic class to reach clinical use, preceding modafinil by approximately a decade in French clinical practice and by 14 years in regulatory terms relative to the United States Food and Drug Administration approval of modafinil in 1998 [3, 4].

The term "eugeroic" (from the Greek eu, good, and egersis, arousal) was coined in 1988 by Michel Jouvet to characterize the distinctive pharmacological profile of adrafinil and modafinil: sustained, dose-dependent promotion of wakefulness and vigilance without the peripheral sympathomimetic effects, psychomotor agitation, rebound hypersomnia, or addictive liability characteristic of amphetamines and other classical psychostimulants [9]. The eugeroic profile distinguished adrafinil from existing treatments for excessive daytime sleepiness and was the principal pharmacological claim on which the compound was marketed.

Adrafinil is converted to modafinil in the liver through enzymatic hydrolysis of the hydroxamic acid moiety, a process that also generates the inactive metabolite modafinilic acid [6]. The pharmacological activity of adrafinil is therefore mediated principally by modafinil, which inhibits the dopamine transporter (DAT) with low affinity but high selectivity, producing elevated extracellular dopamine concentrations that drive wakefulness through a polysynaptic cascade involving D1 and D2 dopamine receptors, lateral hypothalamic orexin neurons, tuberomammillary histaminergic neurons, and cortical glutamatergic and GABAergic circuits [10, 11, 12]. Positron emission tomography studies by Volkow et al. (2009) demonstrated that modafinil at clinical doses (200 to 400 mg) occupies approximately 50 to 57 percent of striatal dopamine transporters in healthy human subjects, an occupancy level comparable to methylphenidate but associated with substantially lower reinforcing effects and abuse potential [13].

The clinical evidence base for adrafinil itself is limited to six principal studies conducted in France between 1979 and the mid-1990s, predominantly in elderly patients with vigilance and attentional complaints [14, 15, 16]. These studies reported statistically significant improvements in attention, wakefulness, self-evaluated vigilance, and depressive symptoms, though the trial designs predated modern regulatory standards for placebo-controlled efficacy demonstration. The compound was marketed in France from 1986 to September 2011, when the Commission d'Autorisation de Mise sur le Marche concluded that the clinical evidence was insufficient to establish benefit and that the adverse effect profile (hepatic enzyme elevations, rare skin reactions) constituted an unfavorable risk-benefit ratio given modafinil availability [17].

Adrafinil is not a controlled substance in the United States, the United Kingdom, Canada, or most other jurisdictions and is widely available as a research compound and unregulated dietary supplement. This monograph documents chemistry, pro-drug metabolism, molecular pharmacology through the modafinil mechanism, pharmacokinetics, preclinical and clinical evidence, sourcing, handling, stack interactions, adverse events, and a structured comparative assessment of five wakefulness-promoting alternatives.

3. Discovery and Development History

3.1 Origin

Adrafinil was discovered in 1974 by chemists Louis Gombert and Roger Assous at Laboratoire Lafon (L. Lafon Ltd.), a small pharmaceutical company headquartered in Maisons-Alfort near Paris, France [3, 4]. The compound was identified during a systematic screening of diphenylmethyl sulfinyl derivatives for analgesic activity. Although adrafinil did not demonstrate the targeted analgesic properties, it produced a dose-dependent increase in spontaneous motor activity in mice that was qualitatively distinct from the hyperactivity produced by amphetamine: the motor activation was sustained, non-stereotyped, and unaccompanied by the peripheral sympathomimetic signs (piloerection, exophthalmos, salivation) characteristic of catecholaminergic stimulants [1, 18].

The compound was passed to Lafon pharmacologists Jacques Duteil and Josette Rambert for extended preclinical characterization. Duteil and Rambert confirmed the wakefulness-promoting properties and the absence of amphetamine-like peripheral effects, establishing adrafinil as a novel pharmacological entity distinct from available psychostimulants [2].

3.2 Early preclinical evaluation

Adrafinil was subsequently provided to Michel Jouvet at the Department of Experimental Medicine, University of Lyon, for evaluation in cats, and to Milhaud and Klein at the Centre d'Etudes et de Recherches de Medecine Aeronautique (CERMA) for evaluation in rhesus monkeys [3, 4]. In cats, adrafinil produced a decrease in total sleep time and an increase in wakefulness as measured by electroencephalographic recordings, without the cortical desynchronization pattern characteristic of amphetamine. In rhesus monkeys (*Macaca mulatta*), a dose of 60 mg/kg approximately doubled nocturnal motor activity, and doses of 90 and 120 mg/kg increased it approximately fourfold [19]. Importantly, no tolerance was observed on repeated administration in the monkey studies, and the activity increase was confined to the waking behavioral repertoire without stereotypy.

3.3 Discovery of modafinil

In April 1976, two years after the discovery of adrafinil, Lafon chemists identified the primary active metabolite CRL-40476, subsequently named modafinil [3]. Modafinil (2-diphenylmethanesulfonylacetamide) displayed the same qualitative pharmacological profile as adrafinil but was more potent per unit dose and longer-lasting in animal models. The recognition that adrafinil was a prodrug of modafinil redirected the Lafon development program: modafinil became the lead compound for clinical development in narcolepsy and excessive daytime sleepiness, while adrafinil was positioned for a lower-acuity geriatric vigilance indication that did not require the same regulatory rigor.

3.4 Clinical testing and French registration

Adrafinil was first tested in human subjects by Michel Jouvet in 1977 to 1978, when he administered the compound to hypersomniac and narcoleptic patients at the Lyon sleep clinic [3, 4]. The results were inconsistent, reflecting both the variable prodrug conversion kinetics and the heterogeneity of the patient population.

Between 1980 and 1995, six clinical studies were conducted in elderly patients (aged 45 years and older, majority older than 65) exhibiting complaints of inattention, drowsiness, memory difficulty, and mild depressive symptoms [14, 15, 16]. The results of these trials, which employed various designs including multicenter double-blind placebo-controlled protocols, provided the basis for French registration. Adrafinil (Olmifon) reached the French market in 1986 for the treatment of vigilance and wakefulness disturbances in the elderly, and a separate indication for narcolepsy was registered in 1985.

3.5 Transition to modafinil and market withdrawal

Modafinil was registered in France in 1994 under the brand name Modiodal for the treatment of narcolepsy and subsequently received United States Food and Drug Administration approval in December 1998 under the brand name Provigil (Cephalon, Inc.) [20]. The availability of modafinil, a more potent and directly acting agent with an extensive controlled-trial evidence base, progressively reduced the clinical rationale for adrafinil.

Cephalon, Inc. acquired Laboratoire Lafon in 2001, gaining the rights to both modafinil and adrafinil. In September 2011, following a regulatory review that found the adrafinil clinical evidence insufficient to establish benefit and the hepatotoxicity signal unfavorable relative to modafinil, adrafinil (Olmifon) was voluntarily withdrawn from the French market [17]. The compound has not been registered in any other jurisdiction.

3.6 Current status

Adrafinil is not a controlled substance in the United States, the United Kingdom, Canada, Australia, or most other jurisdictions, though it is listed on the World Anti-Doping Agency prohibited list as a non-specified stimulant [21]. It is sold by multiple chemical suppliers as a research compound and is available from various online vendors as an unregulated dietary supplement. The compound retains substantial interest in the nootropic and cognitive-enhancement research communities as a legally accessible prodrug of modafinil.

4. Molecular Pharmacology

The pharmacological activity of adrafinil is mediated principally through its conversion to modafinil. The mechanism of action is therefore best understood as a two-stage process: prodrug activation (hydroxamic acid hydrolysis yielding modafinil) followed by the polysynaptic wake-promoting mechanism of modafinil itself.

4.1 Prodrug conversion

Adrafinil is converted to modafinil in the liver through enzymatic hydrolysis of the N-hydroxyl group on the terminal hydroxamic acid moiety [6]. The reaction cleaves the N-O bond to yield modafinil (2-diphenylmethylsulfinylacetamide) and, through a parallel or sequential pathway, modafinilic acid (CRL-40467, 2-diphenylmethylsulfinylacetic acid). Modafinilic acid is pharmacologically inactive and is the principal urinary metabolite of both adrafinil and modafinil [22]. The precise hepatic enzyme(s) responsible for the hydroxamic acid hydrolysis have not been definitively identified; the conversion is understood to involve hepatic microsomal enzymes, potentially including amidases and esterases, rather than the cytochrome P450 system that dominates subsequent modafinil metabolism.

The prodrug conversion imposes a delay of approximately 45 to 60 minutes between oral administration of adrafinil and the onset of pharmacological effects, corresponding to the time required for absorption, hepatic first-pass conversion, and accumulation of modafinil to active plasma concentrations [14]. This delay is the principal pharmacokinetic disadvantage of adrafinil relative to direct modafinil administration.

4.2 Dopamine transporter inhibition

The primary molecular target of modafinil is the dopamine transporter (DAT), a sodium-dependent membrane protein of the solute carrier 6 (SLC6) family that mediates presynaptic reuptake of dopamine from the synaptic cleft [10, 11]. Modafinil binds the DAT with low affinity (K_i approximately 2.3 micromolar) but high selec-

tivity, inhibiting dopamine reuptake and elevating extracellular dopamine concentrations in the nucleus accumbens, caudate, putamen, and prefrontal cortex [10, 23].

The low binding affinity classifies modafinil as an atypical DAT inhibitor, distinct from classical psychostimulants such as amphetamine (which promotes dopamine release through vesicular and transporter-mediated mechanisms), methylphenidate (K_i approximately 0.1 micromolar at DAT), and cocaine (K_i approximately 0.3 micromolar at DAT) [10, 23]. Despite the low affinity, positron emission tomography (PET) studies using [^{11}C]cocaine and [^{18}F]FE-PE2I as DAT radioligands have demonstrated that modafinil at therapeutic doses (200 to 400 mg) produces substantial DAT occupancy: Volkow et al. (2009) reported mean occupancies of 53.8 percent in the caudate, 47.2 percent in the putamen, and 39.3 percent in the nucleus accumbens [13]. Subsequent PET studies confirmed mean striatal DAT occupancies of 51.4 percent at 200 mg and 56.9 percent at 300 mg [24].

The high occupancy at low affinity reflects the sustained plasma concentrations achieved with the long elimination half-life of modafinil and the slow dissociation kinetics of the modafinil-DAT complex. The clinical consequence is that modafinil produces functionally significant dopamine reuptake inhibition sufficient for wakefulness promotion, though with slower onset, lower peak effect, and less reinforcing subjective quality than high-affinity DAT inhibitors.

The essentiality of the DAT mechanism has been established by genetic and pharmacological experiments: in DAT knockout mice, modafinil fails to produce wakefulness [25]; in dopamine D1 and D2 receptor double-knockout mice, the arousal effect is abolished [26]; and in healthy human subjects, pretreatment with the D1/D2 antagonist haloperidol attenuates the modafinil-induced wakefulness [11].

4.3 Downstream orexinergic activation

Modafinil does not bind orexin (hypocretin) receptors directly. However, elevated dopamine in the ventral tegmental area and substantia nigra activates D1 receptors expressed on orexin-positive neurons in the lateral hypothalamus, stimulating orexin release [12, 27]. The orexinergic system is a master regulator of sleep-wake transitions and coordinates the activity of multiple arousal-promoting nuclei. Activation of orexin neurons by modafinil-elevated dopamine produces secondary

activation of downstream targets including the tuberomammillary nucleus (histamine), the locus coeruleus (norepinephrine), the dorsal raphe (serotonin), and the basal forebrain (acetylcholine) [12].

The orexinergic contribution to modafinil-induced wakefulness has been demonstrated by the finding that modafinil produces attenuated but not abolished wakefulness in orexin knockout mice and in orexin neuron-ablated mice, indicating that the orexin pathway is contributory but not essential [28]. The residual wakefulness in these models is attributable to the direct dopaminergic and histaminergic components.

4.4 Histaminergic activation

The tuberomammillary nucleus (TMN) of the posterior hypothalamus is the sole source of neuronal histamine in the brain and is a critical node in the ascending arousal system. Modafinil increases extracellular histamine in the anterior hypothalamus through an orexin-dependent mechanism: orexin neurons project directly to TMN histaminergic neurons, and their activation drives histamine release into widespread cortical projections [29]. Histamine H1 receptor activation in the cortex promotes electroencephalographic desynchronization (the cortical correlate of wakefulness).

Ishizuka et al. (2003) demonstrated that modafinil activates the histaminergic system through orexinergic neurons and that the histaminergic component is partially responsible for the sustained cortical arousal observed with modafinil [29]. Genetic ablation of histamine neurons in mice reduces but does not abolish modafinil-induced wakefulness, confirming the histaminergic pathway as one of several parallel arousal mechanisms [30].

4.5 Glutamatergic and GABAergic modulation

Modafinil increases extracellular glutamate concentrations and decreases extracellular gamma-aminobutyric acid (GABA) concentrations in the medial preoptic area and the posterior hypothalamus [31]. The glutamatergic increase is partly secondary to dopamine-driven orexin release (orexin neurons release glutamate as a co-transmitter) and partly due to direct effects on thalamocortical glutamatergic projections. The GABAergic decrease reflects reduced inhibitory input to arousal-promoting nuclei, potentially through dopamine-mediated disinhibition.

The net effect is a shift in the cortical excitation-inhibition balance toward excitation, promoting sustained wakefulness without the dramatic increases in locomotor activity and sympathetic outflow produced by amphetamine.

4.6 Early alpha-adrenergic hypothesis

The earliest mechanistic investigations of adrafinil, conducted by Duteil et al. (1979), proposed an alpha-1 adrenergic postsynaptic mechanism based on the observation that the central alpha-1 adrenergic antagonists prazosin and phenoxybenzamine blocked adrafinil-induced motor hyperactivity in mice [2]. This hypothesis was the dominant mechanistic framework for approximately 15 years. However, subsequent radioligand binding studies demonstrated that neither adrafinil nor modafinil binds to the alpha-1 adrenergic receptor at pharmacologically relevant concentrations, and the compounds lack the peripheral sympathomimetic effects expected of alpha-1 agonists [10, 32]. The prazosin sensitivity is now interpreted as reflecting the downstream consequences of dopamine-driven noradrenergic activation (the locus coeruleus receives input from dopaminergic and orexinergic neurons) rather than direct alpha-1 receptor agonism. The alpha-adrenergic hypothesis is of historical significance but is not the current consensus mechanism.

4.7 Additional targets

Modafinil weakly inhibits serotonin reuptake (IC₅₀ approximately 35.6 micromolar) and dopamine reuptake (IC₅₀ approximately 6.4 micromolar) and has minimal activity at norepinephrine reuptake (IC₅₀ greater than 500 micromolar) [10]. The serotonin reuptake inhibition is unlikely to contribute meaningfully at clinical concentrations but may be relevant to the modest mood-elevating effects reported in some studies. Modafinil has also been reported to enhance gap junction coupling between cortical interneurons, though the functional significance of this observation is uncertain [33].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Adrafinil is absorbed from the gastrointestinal tract after oral administration. Peak plasma concentrations of adrafinil are reached within approximately 1 hour of oral administration [14]. Oral bioavailability of adrafinil itself has not been precisely determined due to the absence of an intravenous formulation. The compound is converted to modafinil during first-pass hepatic metabolism; peak plasma concentrations of the active metabolite modafinil are typically reached approximately 1.5 to 2.5 hours after adrafinil administration, reflecting the combined absorption and conversion kinetics [6, 14].

A standard oral dose of 300 mg of adrafinil is considered approximately equivalent to 100 to 150 mg of modafinil in terms of the modafinil exposure produced, though substantial inter-individual variability exists [6]. Food modestly delays absorption without significantly affecting total exposure.

5.2 Distribution

Distribution data are available primarily for modafinil rather than for adrafinil itself. Modafinil has an apparent volume of distribution of approximately 0.5 to 0.8 liters per kilogram (approximately 42 liters in a 70 kg adult), indicating moderate tissue distribution [22]. Plasma protein binding of modafinil is approximately 60 percent, predominantly to albumin. Modafinil crosses the blood-brain barrier; central nervous system penetration is confirmed by the reliable central pharmacological effects and by PET imaging studies demonstrating striatal DAT occupancy [13, 24].

5.3 Metabolism

Adrafinil undergoes extensive hepatic metabolism through two parallel pathways [6, 22]:

Pathway 1, hydrolysis to modafinil: The hydroxamic acid is cleaved by hepatic enzymes to yield modafinil (the active metabolite) and hydroxylamine. This pathway is responsible for the pharmacological activity of adrafinil.

Pathway 2, hydrolysis to modafinilic acid: A parallel or sequential hydrolytic pathway converts adrafinil to modafinilic acid (CRL-40467, 2-diphenylmethylsulfinylacetic acid), which is pharmacologically inactive. This pathway represents a metabolic loss that contributes to the lower potency of adrafinil relative to equimolar modafinil.

Once formed, modafinil is further metabolized predominantly through amide hydrolysis to modafinilic acid (the major pathway, accounting for approximately 40 to 50 percent of modafinil metabolism) and through cytochrome P450-mediated pathways [22]. Modafinil is metabolized by CYP3A4 (producing modafinil sulfone, CRL-41056) with minor contributions from other CYP isoforms. Modafinil is a reversible inhibitor of CYP2C19 (K_i approximately 39 micromolar) and a weak inducer of CYP1A2, CYP2B6, and CYP3A4 [34, 35].

The elimination half-life of modafinil produced from adrafinil metabolism is approximately 12 to 15 hours in healthy adults, consistent with the known pharmacokinetics of directly administered modafinil [22]. The S-enantiomer of modafinil (esmodafinil) has a shorter half-life (approximately 3 to 5 hours) than the R-enantiomer (armodafinil, approximately 10 to 17 hours), producing a biphasic elimination profile for the racemic mixture [5].

5.4 Elimination

The primary route of elimination is renal excretion of modafinilic acid and other metabolites. Less than 10 percent of modafinil is excreted unchanged in urine [22]. The contribution of biliary excretion is minor. The pharmacokinetic profile supports once-daily dosing of adrafinil, typically in the morning, though the delayed onset relative to modafinil (approximately 45 to 60 minutes versus 30 to 60 minutes) is a practical consideration.

5.5 Routes of administration

Adrafinil has been studied and used exclusively via the oral route. No intravenous, intramuscular, or other parenteral formulations have been developed or studied. The marketed formulation (Olmifon) was a 300 mg oral tablet. Research-grade ma-

terial is typically administered in oral capsule or powder form.

5.6 Special populations

Pharmacokinetic data in special populations are limited for adrafinil. For the active metabolite modafinil, elderly subjects show modestly reduced clearance; however, the registered adrafinil indication was specifically in elderly patients, and the 300 mg dose was established in this population [14]. Hepatic impairment would be expected to reduce prodrug conversion efficiency and to prolong modafinil elimination, and dose adjustment is prudent in this population. Renal impairment has minimal effect on modafinil clearance. Adrafinil has not been studied in pregnancy or lactation and should be avoided in these populations.

6. Preclinical Pharmacology

6.1 Rodent studies

The initial pharmacological characterization of adrafinil was conducted in mice by the Lafon pharmacology group [1, 18]. Adrafinil produced a dose-dependent increase in spontaneous motor activity that was qualitatively distinct from amphetamine: the activity was non-stereotyped, did not include the circling, rearing, and grooming stereotypies characteristic of high-dose amphetamine, and was not accompanied by peripheral sympathomimetic signs. The motor activity increase was blocked by prazosin and phenoxybenzamine (central alpha-1 antagonists) but not by propranolol (beta-adrenergic antagonist), leading to the original alpha-adrenergic hypothesis [2].

Subsequent studies demonstrated that adrafinil did not produce self-administration behavior in rats at doses that produced self-administration of amphetamine and cocaine, supporting the low abuse liability that would later be confirmed for modafinil in human studies [18]. Adrafinil also did not produce conditioned place preference at wakefulness-promoting doses, further distinguishing it from classical psychostimulants.

A study by Siwak et al. (2003) examined adrafinil effects in aged beagle dogs using a delayed nonmatching-to-position task and reported that adrafinil disrupted performance on this spatial memory task, suggesting that the wakefulness-promoting effects did not translate to cognitive enhancement in this model and that arousal-related interference with cognitive function may occur at higher doses [36].

6.2 Feline studies

Michel Jouvet and colleagues characterized adrafinil effects on the sleep-wake cycle in cats using chronic electroencephalographic, electromyographic, and electrooculographic recordings [9]. Adrafinil produced a dose-dependent increase in waking time and a corresponding decrease in both slow-wave sleep and rapid eye movement (REM) sleep. The wakefulness was qualitatively normal: the cortical electroencephalogram during adrafinil-induced wakefulness resembled physiological waking rather than the forced arousal pattern produced by amphetamine. No re-

bound hypersomnia was observed after drug washout, a finding that contributed to the "eugeroic" characterization and that distinguished adrafinil from amphetamine, which produces rebound sleep increases after cessation [9].

6.3 Primate studies

Milhaud and Klein at CERMA characterized adrafinil in rhesus monkeys (*Macaca mulatta*), demonstrating dose-dependent increases in nocturnal motor activity: a dose of 60 mg/kg approximately doubled nocturnal activity, while doses of 90 and 120 mg/kg increased it approximately fourfold [3, 19]. No tolerance was observed with repeated administration over multiple days, a finding that contrasted with the rapid tolerance development characteristic of amphetamine in similar paradigms.

7. Clinical Evidence Base

7.1 Elderly vigilance and attention studies

The principal clinical evidence for adrafinil consists of six studies conducted in France between 1979 and the mid-1990s in elderly patients with complaints of inattention, drowsiness, poor memory, and mild depressive symptoms [14, 15, 16]. The patient populations were ambulatory and hospitalized individuals aged 45 years and older, with the majority older than 65 years, who exhibited "problems in focusing attention, sleep, memory, and mild depression."

Fontan et al. (multicenter, double-blind, placebo-controlled): This study enrolled 48 subjects residing in senior care facilities, aged 65 years or older, with documented disturbances of vigilance, wakefulness, and attention. Adrafinil at 600 mg twice daily (total daily dose 1200 mg, substantially above the later standard 300 mg dose) for two months produced statistically significant improvements in self-evaluations of vigilance and sleep quality compared to placebo [14, 15].

Additional geriatric studies: The remaining studies evaluated adrafinil at doses of 300 to 900 mg daily in similar elderly populations and reported improvements in vigilance, attention, memory, orientation, depressive symptom scores, fatigue, autonomy, and sociability [14, 15, 16]. The outcome measures were predominantly subjective rating scales and clinician assessments rather than the objective cognitive testing batteries and polysomnographic endpoints that would characterize the modafinil registration trials.

The Milgram et al. (1999) review in CNS Drug Reviews synthesized this evidence and concluded that "human studies indicate that adrafinil has clinical efficacy as a vigilance-promoting and mood-enhancing agent in the elderly," while noting the methodological limitations of the available studies [14].

7.2 Narcolepsy

Michel Jouvet administered adrafinil to hypersomniac and narcoleptic patients in the late 1970s, but results were inconsistent and were not published as formal controlled trials [3, 4]. The narcolepsy indication was nonetheless registered in France

in 1985, though the clinical evidence was limited. By the time modafinil completed its registration program for narcolepsy (formal randomized controlled trials meeting United States and European regulatory standards), adrafinil was no longer competitive for this indication, and modafinil became the standard eugeroic treatment for narcolepsy in all jurisdictions.

7.3 Cognitive endpoints

Adrafinil has not been formally evaluated in randomized controlled trials for cognitive enhancement in healthy subjects or in specific neurocognitive disorders. The reported cognitive improvements in elderly patients (memory, attention, ideation speed) are derived from the geriatric vigilance studies described above and may reflect secondary benefits of improved wakefulness and reduced somnolence rather than direct procognitive effects [14, 15]. The active metabolite modafinil has been more extensively studied for cognitive enhancement in healthy subjects and in clinical populations (sleep deprivation, attention-deficit hyperactivity disorder, depression-related cognitive impairment) with modest positive results, though modafinil is not approved for cognitive enhancement in any jurisdiction [37, 38].

7.4 Regulatory assessment and market withdrawal

In 2011, the French Commission d'Autorisation de Mise sur le Marche reviewed the available clinical studies for adrafinil and was unable to conclude that adrafinil provided clinically meaningful benefit [17]. The committee noted the limited sample sizes, the predominance of subjective outcome measures, the absence of comparator arms, and the methodological limitations of the available trials. Combined with the known adverse-effect profile (hepatic enzyme elevations with chronic use, rare skin reactions, gastrointestinal complaints) and the availability of modafinil as a better-characterized alternative, the committee concluded that the risk-benefit ratio was unfavorable. Adrafinil (Olmifon) was voluntarily withdrawn from the French market in September 2011.

8. Sourcing and Quality Verification

Adrafinil is not available as a pharmaceutical-grade product in any jurisdiction following the 2011 withdrawal of Olmifon. All currently available adrafinil is research-grade or supplement-grade material from chemical suppliers and online vendors.

Research-grade adrafinil is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, MedChemExpress, Santa Cruz Biotechnology, Toronto Research Chemicals, BenchChem, others) at greater than 98 percent purity by HPLC. Supply is typically in milligram to multi-gram quantities as the free base. Pricing varies substantially between research-grade suppliers (approximately \$30 to \$150 per gram) and supplement-grade vendors (often substantially lower per gram in bulk).

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (290.0851 for the protonated species $[M+H]^+$, or 289.0773 monoisotopic for the neutral molecule)
- Nuclear magnetic resonance spectroscopy for structural confirmation, particularly to distinguish adrafinil (hydroxamic acid) from modafinil (amide) and modafinilic acid (carboxylic acid), which share the benzhydryl sulfinyl core
- Melting point determination (159 to 160 degrees Celsius for pure adrafinil)
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis for common synthesis solvents

The supplement-grade adrafinil market carries higher variability and greater risk of contamination, underdosing, substitution with other compounds, or degradation products. Third-party analytical laboratories (Janoshik Analytical, Colmaric Analyticals, others) provide independent confirmation of vendor certificates of analysis. Analytical confirmation is appropriate for any investigation where dose-response precision or safety assessment is important.

9. Reconstitution and Handling

Adrafinil is supplied as a white to off-white crystalline powder. The compound is poorly soluble in water and is typically prepared for research applications in one of the following forms:

Oral administration (research or supplement use): The powder is weighed on an analytical balance and administered in gelatin or vegetable capsules, or dissolved in a small volume of propylene glycol or polyethylene glycol 400. The standard dose range in published studies is 300 to 1200 mg daily; the most commonly used research dose is 300 mg once daily in the morning [14].

In vitro stock solutions: Adrafinil dissolves readily in dimethyl sulfoxide (DMSO) at concentrations up to 50 mg/mL. Stock solutions in DMSO are stable at minus 20 degrees Celsius for at least 6 months. For cell culture applications, the final DMSO concentration in the culture medium should not exceed 0.1 percent (v/v) to avoid solvent cytotoxicity.

Storage: The solid compound should be stored in a sealed container at room temperature (15 to 25 degrees Celsius), protected from moisture. Under these conditions, the compound is stable for at least 2 years. Stock solutions in DMSO should be stored at minus 20 degrees Celsius and protected from light. Aqueous solutions are not recommended due to the low water solubility of adrafinil.

Handling precautions: Adrafinil is not classified as a hazardous substance under standard chemical safety classifications. Standard laboratory personal protective equipment (gloves, laboratory coat, eye protection) is appropriate for handling.

10. Stack Interactions and Combinations

Adrafinil interacts with several drug classes through its hepatic metabolism to modafinil and through the downstream pharmacological effects of modafinil. Investigators conducting research with adrafinil, especially in chronic dosing regimens or in combination with other research compounds, should consider:

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, grapefruit juice) can increase modafinil exposure by reducing CYP3A4-mediated clearance. Concurrent use may require dose adjustment of adrafinil or monitoring for enhanced effects and adverse events.

CYP3A4 inducers: Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) may reduce modafinil exposure. Concurrent dosing may compromise the efficacy of adrafinil at standard doses.

CYP2C19 substrates: Modafinil is a reversible inhibitor of CYP2C19 (K_i approximately 39 micromolar) and may increase plasma concentrations of CYP2C19 substrates, including diazepam, phenytoin, omeprazole, clopidogrel (prodrug activation), and some antidepressants (citalopram, escitalopram) [34, 35]. Concurrent use warrants monitoring.

Hormonal contraceptives: Modafinil induces CYP3A4 at clinical doses, which may reduce the efficacy of ethinyl estradiol-containing oral contraceptives. Alternative or additional contraceptive methods should be considered during adrafinil use and for one month after discontinuation [22].

Other stimulants and wakefulness-promoting agents: Concurrent use with caffeine, amphetamines, methylphenidate, or other modafinil formulations produces additive stimulant effects and may increase the risk of insomnia, tachycardia, and anxiety. The combination of adrafinil with direct modafinil is pharmacologically redundant and is not recommended.

Dopaminergic agents: Concurrent dopamine agonists (pramipexole, ropinirole) or dopamine precursors (levodopa) may produce additive dopaminergic effects. Concurrent dopamine antagonists (antipsychotics, metoclopramide) may attenuate

the wakefulness-promoting effects of adrafinil.

Hepatotoxic agents: Given the hepatic enzyme elevation signal associated with chronic adrafinil use, concurrent administration with other hepatotoxic agents (acetaminophen at high doses, statins, certain anticonvulsants, alcohol) should be approached with caution and with monitoring of hepatic function.

Serotonergic agents: Modafinil weakly inhibits serotonin reuptake. The combination with serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, or other serotonergic agents is unlikely to produce clinically significant serotonergic interaction at standard doses, but monitoring is appropriate at higher doses or in patients with serotonergic sensitivity.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events reported in clinical studies and in post-marketing surveillance of adrafinil at doses of 300 to 900 mg daily include [14, 15, 17]:

- Insomnia (dose-dependent; the most common adverse event, reflecting the primary pharmacological action and particularly prominent with late-day dosing)
- Headache (5 to 10 percent)
- Nausea (3 to 8 percent)
- Stomach pain and gastrointestinal discomfort (3 to 5 percent)
- Anxiety and nervousness (2 to 5 percent)
- Dizziness (1 to 3 percent)
- Dry mouth (1 to 3 percent)

These adverse-event rates are broadly similar to those reported for modafinil at equipotent doses, though the adrafinil adverse-event data are derived from smaller and less rigorously controlled studies.

11.2 Hepatotoxicity

Hepatotoxicity is the most clinically significant safety concern specific to adrafinil and was a principal factor in the 2011 market withdrawal decision [17]. Chronic adrafinil use (daily administration over periods of weeks to months) has been associated with elevations in hepatic transaminases (serum glutamic-oxaloacetic transaminase [SGOT/AST], serum glutamic-pyruvic transaminase [SGPT/ALT]), gamma-glutamyl transpeptidase (GGT), and hepatic alkaline phosphatase [14, 17].

The mechanism of hepatotoxicity is not definitively established but is plausibly related to the hepatic conversion process itself: the hydrolysis of the hydroxamic acid moiety to yield modafinil may generate reactive intermediates or impose metabolic stress on hepatic enzyme systems that direct modafinil administration does not [6]. Hydroxylamine, a byproduct of hydroxamic acid hydrolysis, is a

known hepatotoxin at high concentrations, and the chronic generation of hydroxylamine through repeated adrafinil dosing may contribute to cumulative hepatic injury.

Modafinil itself has been associated with rare hepatic injury (the LiverTox database classifies modafinil hepatotoxicity as rare and usually mild), but the hepatotoxicity signal for adrafinil appears to be more pronounced, consistent with the additional metabolic burden imposed by the prodrug conversion step [39].

Investigators using adrafinil chronically should monitor hepatic function (ALT, AST, GGT, alkaline phosphatase, bilirubin) at baseline and at regular intervals during dosing.

11.3 Skin reactions

Rare skin reactions have been reported with adrafinil use, including rash, pruritus, and urticaria [17]. These are consistent with the skin reaction profile of modafinil, which includes rare serious cutaneous adverse reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis) documented in postmarketing surveillance of modafinil and armodafinil [22]. The frequency of serious skin reactions with adrafinil specifically has not been characterized due to the limited clinical database, but any unexplained rash during adrafinil use should prompt immediate discontinuation and evaluation.

11.4 Cardiovascular effects

Modafinil produces modest increases in heart rate and blood pressure at clinical doses, reflecting the downstream sympathomimetic consequences of elevated dopaminergic tone [22]. These effects are generally mild and well tolerated in healthy subjects but may be clinically significant in patients with pre-existing cardiovascular disease. Adrafinil would be expected to produce similar cardiovascular effects at equipotent doses, though cardiovascular monitoring data from adrafinil clinical studies are limited.

11.5 Psychiatric effects

Anxiety, nervousness, agitation, and insomnia are dose-dependent adverse events reflecting the primary pharmacological mechanism. Rare psychiatric adverse events reported with modafinil (and potentially applicable to adrafinil) include mania or hypomania in patients with bipolar disorder, psychotic symptoms at high doses, and suicidal ideation [22]. Adrafinil should be used with caution in patients with a history of psychiatric illness.

11.6 Abuse potential

Modafinil has lower abuse potential than classical psychostimulants despite comparable DAT occupancy, a dissociation attributed to the slow pharmacokinetic onset, the low DAT binding affinity, and the absence of the rapid dopamine surge that drives the reinforcing subjective effects of cocaine and amphetamine [13, 40]. Modafinil is classified as a Schedule IV controlled substance in the United States. Adrafinil, with its additional delay imposed by prodrug conversion, would be expected to have even lower acute reinforcing potential, and it is not a controlled substance in most jurisdictions. However, chronic adrafinil use does produce tolerance in some individuals, and psychological dependence has been reported anecdotally.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five wakefulness-promoting and eugeroic agents against adrafinil, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal alternatives that an investigator considering adrafinil for research or cognitive-enhancement applications would evaluate.

12.1 Modafinil (CRL-40476, Provigil)

Mechanism: Direct-acting atypical DAT inhibitor. Same pharmacological mechanism as adrafinil's active metabolite, without the prodrug conversion step.

Development trajectory: Modafinil was identified at Laboratoire Lafon in 1976 as the active metabolite of adrafinil and was independently developed for narcolepsy, obstructive sleep apnea hypopnea syndrome, and shift work sleep disorder [20]. FDA approval was granted in December 1998 (Provigil, Cephalon). The compound has been approved in more than 20 countries and has generated an extensive clinical trial literature encompassing narcolepsy, shift work disorder, cognitive enhancement, depression augmentation, attention-deficit hyperactivity disorder, fatigue in multiple sclerosis, and military operational applications [37, 38].

Novelty: Low relative to adrafinil (same active compound). The novelty of the eugeroic mechanism itself was high when first characterized.

Effect size: Substantial for wakefulness endpoints. In narcolepsy trials, modafinil 200 to 400 mg reduced sleep latency on the Maintenance of Wakefulness Test by approximately 2 to 3 minutes compared to placebo, with effect sizes (Cohen's d) of approximately 0.5 to 0.8 across studies [20]. Cognitive enhancement effect sizes in non-sleep-deprived healthy subjects are modest (Cohen's d approximately 0.1 to 0.3) [37].

Promising potential: High. The compound is an established, registered medicine with extensive clinical infrastructure. Generic modafinil is available at low cost in most jurisdictions.

Side-effect profile: Well characterized. Principal adverse events are headache, nausea, insomnia, anxiety, and dizziness at moderate frequencies. Rare serious events include Stevens-Johnson syndrome, angioedema, and psychiatric exacerbations. Hepatotoxicity signal is lower than adrafinil [22, 39].

Overall validation: Very high. Modafinil is the most extensively validated eugeroic agent, with multiple Phase 3 registration trials, large-scale postmarketing surveillance, and thousands of published studies.

Comparison to adrafinil: Modafinil is superior to adrafinil on essentially all practical dimensions: faster onset, higher potency per milligram, better characterized pharmacokinetics, lower hepatotoxicity signal, extensive regulatory validation, and wider availability as a registered medicine. Adrafinil's sole practical advantage is its uncontrolled legal status in most jurisdictions, which permits purchase without a prescription. This regulatory asymmetry is the principal driver of continued adrafinil use despite the pharmacological inferiority of the prodrug relative to the active compound.

12.2 Armodafinil (R-modafinil, Nuvigil)

Mechanism: The R-enantiomer of modafinil, with the same DAT inhibition mechanism. Armodafinil has a longer elimination half-life (10 to 17 hours) than racemic modafinil (approximately 12 to 15 hours for the racemate, reflecting the rapid elimination of the S-enantiomer) and produces more sustained plasma concentrations with once-daily dosing [5].

Development trajectory: Developed by Cephalon as a lifecycle extension of modafinil. FDA approval was granted in June 2007 for narcolepsy, obstructive sleep apnea, and shift work disorder (Nuvigil, Cephalon/Teva) [5].

Novelty: Low. Single-enantiomer development of an existing racemate.

Effect size: Comparable to racemic modafinil for wakefulness endpoints, with modestly more sustained effects in the late afternoon and evening, attributed to the longer half-life of the R-enantiomer [5]. Cognitive enhancement effect sizes are comparable to modafinil.

Promising potential: Moderate. The compound is registered and available as a generic. Clinical differentiation from racemic modafinil is modest.

Side-effect profile: Similar to modafinil. The longer half-life may increase the risk of insomnia with late dosing [5].

Overall validation: High. Multiple Phase 3 registration trials with positive outcomes.

Comparison to adrafinil: Armodafinil shares modafinil's advantages over adrafinil (faster onset, lower hepatotoxicity, regulatory validation) and offers a modestly longer duration of action. Adrafinil's advantage is limited to uncontrolled legal status.

12.3 Pitolisant (Wakix)

Mechanism: Selective histamine H3 receptor inverse agonist and antagonist. By blocking the presynaptic H3 autoreceptor on tuberomammillary histaminergic neurons, pitolisant disinhibits histamine synthesis and release, promoting wakefulness through the histaminergic arousal pathway [41]. The mechanism is distinct from the dopaminergic mechanism of the afinil class.

Development trajectory: Developed by Bioprojet. FDA approval was granted in August 2019 for narcolepsy with or without cataplexy, and in October 2020 for obstructive sleep apnea [41].

Novelty: High. The H3 receptor mechanism represents a genuinely different approach to wakefulness promotion than dopaminergic reuptake inhibition.

Effect size: Moderate. In the HARMONY 1 Phase 3 trial, pitolisant 36 mg reduced the Epworth Sleepiness Scale score by approximately 3 points more than placebo in narcolepsy patients [41]. Effect sizes are broadly comparable to modafinil in head-to-head comparisons, though direct comparative trials are limited.

Promising potential: Moderate to high. The compound is registered and commercially available, with growing clinical use.

Side-effect profile: Principal adverse events are headache, insomnia, and nausea; the gastrointestinal and hepatic burden is lower than adrafinil. QT prolongation has been reported at supratherapeutic doses [41].

Overall validation: Moderate. Less extensive postmarketing experience than modafinil, but growing.

Comparison to adrafinil: Pitolisant offers a mechanistically distinct alternative with a favorable hepatic safety profile relative to adrafinil. It is prescription-only and controlled in some jurisdictions.

12.4 Caffeine

Mechanism: Non-selective adenosine A1 and A2A receptor antagonist. Blocking the sleep-promoting effects of adenosine at A2A receptors on ventrolateral preoptic area neurons disinhibits arousal-promoting pathways [42].

Development trajectory: Caffeine is the most widely consumed psychoactive compound globally. It is not a registered medicine for wakefulness promotion in most jurisdictions but is available in military sustained-operations programs as an approved fatigue countermeasure.

Novelty: Very low. The oldest and most broadly studied wakefulness-promoting compound.

Effect size: Small to moderate for sustained wakefulness in sleep deprivation paradigms; effect sizes for cognitive enhancement are modest and subject to rapid tolerance (3 to 5 days of daily use) [42].

Promising potential: Not applicable; the compound is universally available and extensively studied.

Side-effect profile: Anxiety, tachycardia, gastrointestinal distress, and insomnia at moderate doses. Dependence and withdrawal (headache, fatigue) develop rapidly. Hepatotoxicity is not a concern at standard doses [42].

Overall validation: Very high for acute wakefulness; limited for sustained cognitive enhancement due to tolerance.

Comparison to adrafinil: Caffeine offers immediate availability, very low cost, and no hepatotoxicity signal. Adrafinil offers a longer duration of action, less tolerance development, and a potentially more sustained wakefulness effect. For research applications requiring sustained vigilance promotion without rapid tolerance, adrafinil (through its modafinil metabolite) has a mechanistic advantage.

12.5 Flmodafinil (CRL-40,940, Lauflumide, Bisfluoromodafinil)

Mechanism: Bisfluoro derivative of modafinil. The compound is a more potent DAT inhibitor than modafinil, with additional norepinephrine transporter (NET) inhibitory activity and potentially enhanced oral bioavailability [43]. The bisfluorination of the benzhydryl ring increases lipophilicity and may enhance blood-brain barrier penetration.

Development trajectory: Flmodafinil was identified in the Lafon/Cephalon research program as a modafinil derivative with enhanced potency. It has not been approved for clinical use in any jurisdiction and has not completed formal clinical trials. The compound is sold as a research chemical and unregulated supplement.

Novelty: Low to moderate. A structural modification of modafinil within the established benzhydryl sulfinyl class.

Effect size: Preclinical data suggest higher potency per milligram than modafinil, but no controlled human efficacy data are available.

Promising potential: Low. No clinical development program. Regulatory status is uncertain.

Side-effect profile: Not characterized in formal clinical studies. Expected to resemble modafinil with possible differences related to the enhanced NET inhibitory activity (potentially more sympathomimetic effects).

Overall validation: Very low. Preclinical data only; no published controlled human trials.

Comparison to adrafinil: Flmodafinil shares the uncontrolled legal status that drives adrafinil use but offers direct activity without prodrug conversion, potentially higher potency, and no hydroxamic acid metabolism burden. However, the complete absence of human clinical data and the uncertain regulatory status make flmodafinil a less validated choice than adrafinil, which at least has the historical French clinical database and the extensive modafinil literature to support mechanism-of-action inferences.

12.6 Comparator summary

The five comparators occupy distinct positions in the wakefulness-promotion pharmacology space. **Modafinil** is the direct active metabolite of adrafinil and is superior on essentially every practical dimension; it is the benchmark eugeroic against which adrafinil and all other comparators are measured. **Armodafinil** offers marginal pharmacokinetic advantages over racemic modafinil. **Pitolisant** represents a genuinely novel mechanism (H3 inverse agonism) with a favorable hepatic safety profile. **Caffeine** is universally available but limited by rapid tolerance. **Flmodafinil** is a more potent modafinil derivative without clinical validation.

Adrafinil occupies a specific niche in this landscape: it is the only compound that provides access to the modafinil mechanism through a legally uncontrolled pro-drug in most jurisdictions. This regulatory advantage is the compound's principal practical differentiator. From a pharmacological standpoint, adrafinil is inferior to direct modafinil administration on every measured parameter (onset, potency, hepatotoxicity, clinical validation). Investigators with access to prescription modafinil should prefer it over adrafinil. Investigators using adrafinil for research purposes should be aware that the pharmacological effects are attributable to the modafinil metabolite, that the hepatic conversion imposes a metabolic burden not present with direct modafinil, that the clinical evidence base for adrafinil itself is limited, and that hepatic monitoring is appropriate with chronic use.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Adrafinil is not approved by any regulatory authority for human use following the 2011 voluntary withdrawal of French marketing authorization. The compound is sold as a research-grade preparation; investigators should obtain analytical confirmation of identity and purity on every lot.