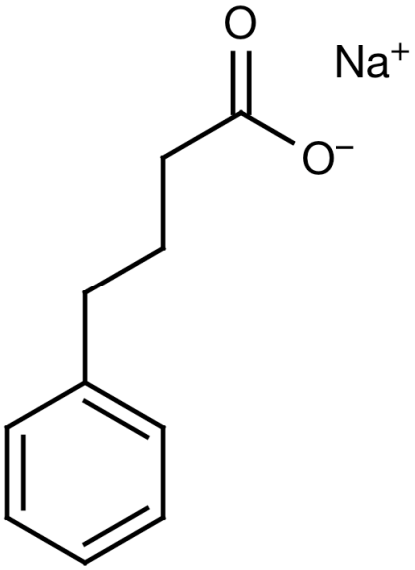
# CINAPS Compound Dossier

# Phenylbutyrate




9/26/2008

National Institute of Neurological Disorders and Stroke

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# I. Compound Information

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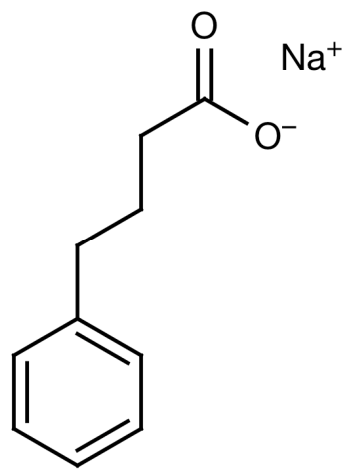
| **Common name** | Phenylbutyrate |
| **Structure** |  |

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|---|---|---|---|---|---|
| **PubChem ID** | 5258 | **MF** | $C_{10}H_{11}Na\ O_2$ | **FW** | 186.18 |
| **CASRN** | 1716-12-7 | **Polar surface area** | 40.13 | **logP** | -1.04 |

| | |
|---|---|
| **IUPAC name** | Sodium 4-phenylbutanoate |
| **Other names** | Buphenyl® |
| **Drug class** | Histone deacetylase inhibitor |
| **Notes** | |
| **Development status** | |

# II. Rationale

## IIa. Scientific Rationale / Mechanism

Histone deacetylases (HDACs) catalyze the removal of acetyl groups from histones resulting in compaction of chromatin, thus silencing transcription probably by preventing the contact of transcription factors, regulatory complexes and RNA polymerases with the DNA (**Langley, 2005**). HDAC inhibitors such as (sodium) phenylbutyrate, valproic acid and trichostatin result in hyperacetylation of the histones and enhanced transcription leading to a greater resistance to cellular stress, possibly inducing the expression of anti-mitotic and anti-apoptotic genes such as p21 and HSP-70 (**Leng, 2008**). Leng (2006 and 2008) demonstrated that the HDAC inhibitor, valproic acid, provided neuroprotection against glutamate-induced excitotoxicity in cerebellar granule cell preparations. This appeared to involve inhibition of glycogen synthase kinase-3 (**Leng, 2008**) as well a possibly neuroprotective role for low levels of normal alpha-synuclein (**Leng, 2006**). This latter conclusion stands in an interesting contrast to the currently discussed role of alpha-synuclein aggregation in Lewy Bodies and Lewy neurites. Perhaps critical to the difference in the findings of Leng, however, is the role of the more readily aggregating mutant alpha-synucleins (A53T, A30P and E46K) that are thought to be highly important role players in familial Parkinson's disease (**Leng, 2006**; **Recchia, 2008**).

Specific demonstrations of the neuroprotective potential of (sodium) phenylbutyrate in models of Parkinson's disease indicate great therapeutic potential for HDAC inhibition and this molecule in particular. Gardian demonstrated a clear protective role for phenylbutyrate in an MPTP mouse model of Parkinsonian-like loss of substantia nigral dopamine, DOPAC and HVA and tyrosine-hydroxylase immunoreactivity (**Gardian, 2004**). In 2007, Inden provided further support for this neuroprotective activity of phenylbutyrate with the attenuation of many components of rotenone-induced deficits in the substantia nigra of rats. In this latter study, however, high daily doses (120 mg/kg) for 30 days (alongside 30 daily rotenone doses) was required to produce significant neuroprotection (**Inden, 2007**).

Further to these animal models, Cudkowicz reported a successful Phase 2 study wherein 9 g/day (and higher) doses of phenylbutyrate produced increased blood histone acetylation in ALS patients - suggesting a capability to achieve neuroprotective efficacy following oral dosing (**Cudkowicz, 2008**).

## IIb. Consistency

n/a

# III. Efficacy (animal models of Parkinson's disease)

## IIIa. Animal Models: Rodent

There are 2 reports of the effectiveness of phenylbutyrate in rodent models of Parkinson's disease. Gardian demonstrated a significant protection of dopamine, DOPAC and HVA levels in the substantia nigra pars compacta (SNpc) of mice that had received MPTP (**Gardian, 2004**). Dosing of 250 mg/kg/day phenylbutyrate daily from 1 day prior to MPTP administration through 7 days following MPTP also produced a significant attenuation in the loss of tyrosine-hydroxylase immunoreactivity in the SNpc. The authors discuss the relevance of this data in the context of a neuroprotective activity of HDAC inhibitors in general, although no data to support this mechanism of action is provided.

Using the rotenone (30 daily doses) model of Parkinsonian mid-brain deficits, Inden demonstrated significant neuroprotective activity of phenylbutyrate at 120 mg/kg/day (for 30 days with rotenone) but not at 15 or 40 mg/kg/day (**Inden, 2007**). Phenylbutyrate protected against the loss of tyrosine-hydroxylase immunoreactive neurons in the striatum, and the loss of striatal dopamine while also attenuating the rotenone-induced alpha-synuclein aggregation and immunoreactivity and attenuating ER-stress and the resulting increase in GRP78 and decrease in procaspase-12. Phenylbutyrate also prevented the rotenone-induced up-regulation of DJ-1 and significantly restored performance on the accelerating rotorod.

## IIIb. Animal Models: Non-human primates

n/a

# IV. Efficacy (Clinical and Epidemiological Evidence)

## IVa. Clinical studies

Sodium phenylbutyrate is currently approved and marketed by Ucyclyd Pharma as Buphenyl(R) (www.buphenyl.com) as an adjunctive therapy for treatment of urea cycle disorders (UCD). As described in the approved prescribing information (http://www.medicis.com/products/pi/pi_buphenyl.pdf) the metabolism and excretion of phenylbutyrate clears waste nitrogen with the same efficiency as normal urea production would (i.e. 2 nitrogens per molecule excreted). Thus critical components of the clinical utility, safety and tolerability of phenylbutyrate are already available.

Researchers at Massachusetts General Hospital have recently completed an open-label Phase 2 study of sodium phenylbutyrate in 40 ALS patients. They showed that 9 g/day was "therapeutically efficient in improving histone acetylation levels" as determined from blood histone acetylation levels. The majority of patients tolerated phenylbutyrate up to the highest dose tested (21 g/day) - 26 patients completed the full 20-week treatment phase (**Cudkowicz, 2008**).

In the period between the approval of Buphenyl® and this 2008 report in ALS, many early stage (Phase 1) studies have been pursued with a focus on solid tumors. The information gleaned from these, high dose, studies does not assess any neuroprotective potential and does not expand on the adverse effect profile described in the original Buphenyl® documentation. As such no in depth review of these studies is included here except to acknowledge the scope of clinical experience with phenylbutyrate.

## IVb. Epidemiological evidence

n/a

## V. Relevance to other neurodegenerative diseases

Cudkowicz demonstrated the safety and tolerability of phenylbutyrate at doses up to 21 g/day in 26 Amyotrophic Lateral Sclerosis (ALS) patients (**Cudkowicz, 2008**). Owing the cohort size and limitations of the available clinical measures, no definitive statement to the neuroprotective effects of phenylbutyrate could be made from this study. However, it is clear that phenylbutyrate is well tolerated by ALS patients (as well as in the patients with Urea Cycle Disfunction or various forms of solid tumor) that the potential to pursue phenylbutyrate in vulnerable patient populations (young or old) is a viable proposition.

In addition the generalized neuroprotective mechanism of HDAC inhibition lends itself well to a number of neurodegenerative disorders. Indeed, Petri has demonstrated an additive neuroprotective effect of HDAC inhibition and catalytic antioxidants in a transgenic mouse model of ALS that implies great utility for this mechanism of action within neurodegenerative diseases (**Petri, 2006**).

# VI. Pharmacokinetics

## VIa. General ADME

The prescribing information for Buphenyl® describes the following clinical pharmacokinetics:

Peak plasma levels of phenylbutyrate occur within 1 hour after a single 5g (tablet) dose with a Cmax of 218 µg/mL under fasting conditions. The powder form provides for a similar Tmax but a slightly lower Cmax (195 µ/mL). Phenylbutyrate is metabolized to phenylacetate and subsequently to phenylacetylglutamine (the pivotal part in its role in UCD). Both phenylbutyrate and phenylacetate are detectable in plasma 15 and 30 minutes following dosing. Phenyacetylglutamine was detected shortly thereafter. Cmax (µ/mL), Tmax (hours) and elimination half-life (hours) were 195, 1.00 and 0.76 respectively for phenylbutyrate and 45.3, 3.55 and 1.29 respectively for phenylacetate (following tablet dosing). Major metabolism sites are the liver and kidneys. The majority of phenylbutyrate is excreted by the kidneys (80-100%) as phenylacetylglutamine within 24 hours of dosing.

Gender differences: Exposure parameters (Cmax and AUC) were 30-50 percent higher in females than in males.

Kasumov describes additional (human and rat) metabolites to phenylacetate / phenylacetylglutamine, namely *R*- and *S*-3-hydroxy-4-phenylbutyrate, phenylacetone, and 1-phenyl-2-propanol, 4-phenyl-*trans*-crotonate and 4-phenyl-3-hetobutyrate. In contrast to the existing prescribing information, Kasumov suggests that only 50% of phenylbutyrate is excreted as phenylacetylglutamine (**Kasumov, 2004**).

## VIb. CNS Penetration

Implicit in the reports of efficacy in animal models of neurodegenerative disease and clinical trials for the treatment of CNS tumors (e.g., gliomas) is the ready brain availability of phenylbutyrate.

Phenylbutyrate distributes into the CSF of non-human primates following i.v. administration (**Berg, 2001**).

**VIc. Calculated log([brain]/[blood]) (Clark Model):** -0.61

### VIIa. Safety and Tolerability

The prescribing information for Buphenyl® indicates neurotoxicity of subcutaneous phenylacetate (the primary metabolite of phenylbutyrate) in rat pups at doses of 190-474 mg/kg. The major effects reported were decreased proliferation and increased loss of neurons, reduced CNS myelin, retarded cerebral synapse maturation and reduced cerebral functioning nerve terminals. Prenatal exposure of rat pups produced lesions in layer 5 of the cortical pyramidal cells with longer, and a reduced number, of dendritic spines. According to Ucyclyd Pharma, no carcinogenicity, mutagenicity or fertility studies had been completed with phenylbutyrate.

Current clinical trials would suggest that there is an appreciable human safety window, with studies currently being reported using doses up to 45 g/day in solid tumor studies. The clinical MTD in a 2001 study in acute myeloid leukemia and myelodysplastic syndromes was 375 mg/kg/day as a continuous infusion (infusions were continued for a 7-day period at this dose level). Dose-limiting toxicity in this study was predominantly observed as reversible neuro-cortical toxicity indicated by somnolence, and confusion and accompanied by clinically significant hypokalemia, hyponatremia and hyperuricemia (**Gore, 2001**; **Carducci, 2001**).

The clinical doses currently approved for chronic management of UCD are 450-600 mg/kg/day as either an oral tablet or powder. Typically Buphenyl® is indicated for children weighing more than 20 kg and adults. The prescribing information for Buphenyl® and the MayoClinic.com summary of potential side effects indicate the following potential adverse reactions:

**More common**

Change in frequency of breathing; Lack of or irregular menstruation; Mood or mental changes; Muscle pain or twitching; Nausea or vomiting; Nervousness or restlessness; Lower back, side or stomach pain; Swelling of feet or lower legs; Unpleasant taste; Unusual tiredness or weakness

**Less common**

Chills; Fever; Joint Pain; Sore Throat; Unusual bleeding or bruising

**Rare**

Convulsions (seizures); Dizziness; Dryness of mouth; Fast, slow or irregular heart beat; Increased blood pressure; Increased thirst; Irritability; Muscle cramps; Rectal bleeding; Swelling of face; Unusual weight gain; Weak pulse.

### VIIb. Drug Interaction Potential

Owing to the high doses used in UCD, the sodium content of the phenylbutyrate dose presents additional risks both in terms of complications related to other conditions (e.g., heart disease or kidney failure) as well complications related to drugs impacting kidney function (e.g., Probenecid is known to inhibit renal transport of organic compounds and so may affect the renal excretion of Buphenyl® and its metabolites) (**DailyMed, 2007**).

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