

## Pharmacokinetics of (6S)-5-Methyltetrahydrofolate dicholine salt compared to folic acid: a randomized double-blind single dose cross-over study

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**Supplementary Table S1.** Mean and SD of plasma concentration of total folate and (6S)-5-MethylTHF after single oral dose of folic acid or (6S)-5-MethylTHF-2Chol

| time [h] | Plasma total folate concentrations (nmol/L) |      |                                      |      | Plasma (6S)-5-MethylTHF concentrations (nmol/L) |      |                                      |      |
|----------|---|------|--------------------------------------|------|---|------|--------------------------------------|------|
|          | Folic acid<br>n = 24                        |      | (6S)-5-MethylTHF-<br>2Chol<br>n = 24 |      | Folic acid<br>n = 24                            |      | (6S)-5-MethylTHF-<br>2Chol<br>n = 24 |      |
|          | Mean  | SD   | Mean                                 | SD   | Mean  | SD   | Mean                                 | SD   |
| 0        | 14.4  | 5.3  | 14.5                                 | 5.7  | 13.1  | 6.0  | 13.2                                 | 5.3  |
| 0.25     | 14.6  | 5.6  | 19.4                                 | 8.0  | 14.3  | 6.5  | 19.9                                 | 8.5  |
| 0.5      | 18.7  | 10.4 | 33.1                                 | 13.1 | 15.2  | 7.6  | 40.1                                 | 17.3 |
| 1        | 26.6  | 12.7 | 36.1                                 | 9.6  | 19.1  | 10.1 | 45.9                                 | 16.5 |
| 1.5      | 25.4  | 9.2  | 31.9                                 | 9.2  | 21.7  | 10.5 | 38.8                                 | 14.0 |
| 2        | 23.4  | 7.8  | 28.4                                 | 7.6  | 21.7  | 9.8  | 31.8                                 | 12.8 |
| 3        | 20.8  | 6.3  | 24.8                                 | 7.0  | 20.1  | 7.6  | 27.6                                 | 10.3 |
| 4        | 19.4  | 5.9  | 22.3                                 | 6.7  | 18.9  | 7.8  | 25.2                                 | 9.1  |
| 6        | 18.6  | 5.2  | 19.9                                 | 5.7  | 17.4  | 5.6  | 21.0                                 | 7.1  |
| 8        | 17.5  | 5.3  | 18.8                                 | 5.1  | 16.4  | 5.8  | 18.8                                 | 6.2  |
| 24       | 15.1  | 4.8  | 15.0                                 | 5.4  | 14.0  | 5.0  | 14.5                                 | 6.3  |

**Supplementary Table S2.** Characteristics of (6S)-5-MethylTHF-2Chol compared to other folate forms

| Property   | Folic acid     | (6S)-5-MethylTHF-<br>Calcium    | (6S)-5-MethylTHF-<br>Glucosamine | (6S)-5-MethylTHF-<br>2Chol |
|--|----------------|---------------------------------|----------------------------------|----------------------------|
| Solid structure  | crystalline    | crystalline                     | crystalline or<br>amorphous      | crystalline                |
| Solubility in H <sub>2</sub> O<br>(H <sub>2</sub> O/ pH 7) | 0.01 mg/mL [1] | 10 mg/mL [2]                    | ~1000 mg/mL [3]                  | 650 mg/mL                  |
| (H <sub>2</sub> O/ pH 3)                                   | insoluble      | n/a                             | n/a                              | 40 mg/mL*                  |
| Folate form  | Oxidized form  | Reduced form                    | Reduced form                     | Reduced form               |
| Stability (solid,<br>dry)                                  | good           | good (cryst.)/ fair<br>(amorph) | fair (amorph)                    | good (cryst.)              |

\*tested concentration (higher concentrations not tested).

### Table S3: Abbreviations and synonyms of folate salts

The following Names and synonyms are used in this manuscript:

(6S)-5-MethylTHF = (6S)-5-Methyltetrahydrofolic acid, alternative names: L-Methylfolate or L-5- Methylfolate  
(6S)-5-MethylTHF-2Chol = Dicholine (6S)-5-Methyltetrahydrofolate salt, alternative name: L-MTHF di Choline, L-Methylfolate 2Chol, Optifolin+®

(6S)-5-MethylTHF-Ca = Calcium (6S)-5-Methyltetrahydrofolate salt, alternative name: Calcium L- Methylfolate

(6S)-5-MethylTHF-Na = Sodium (6S)-5-Methyltetrahydrofolate salt, alternative name: Sodium L-Methylfolate

(6RS)-5-MethylTHF-Ca= Calcium racemic 5-Methyltetrahydrofolate, alternative name: Calcium D/L-Methylfolate  
Folic acid = Pteroylmonoglutamic acid

### References

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