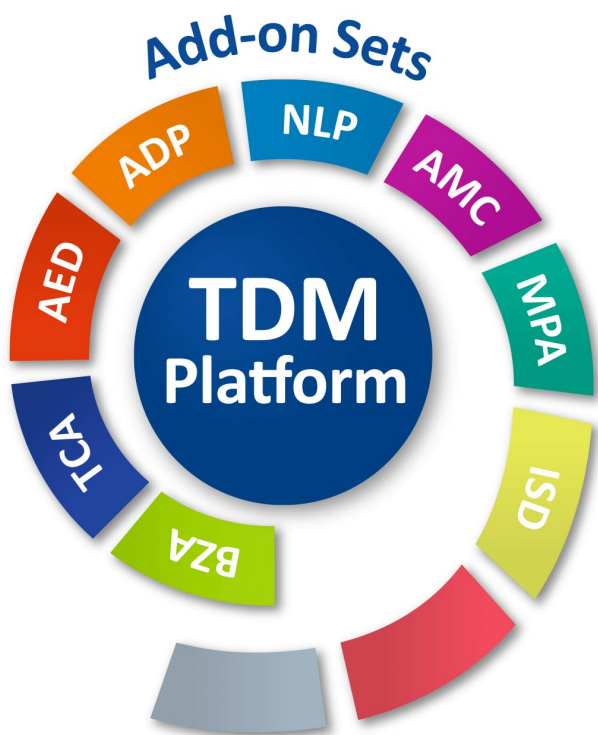


# Benzodiazepines in Serum/Plasma



### Benzodiazepines

The "ClinMass® TDM Kit System" is based on a universal TDM Platform (order no. MS9000), which can be used with various Add-on Sets for the Therapeutic Drug Monitoring (TDM).

The ClinMass® Add-on Set for Benzodiazepines (order no. MS9500) is intended for the determination of Benzodiazepines from human serum or plasma.

- + assist in identifying/confirming and managing of withdrawal syndrome
- + monitoring tapering regimens
- + monitoring of age-related dose adjustment

### Therapeutic Drug Monitoring (TDM)

#### Increasing recommendation in

- + conditions with a small therapeutic range
- + optimisation of a personalised pharmacotherapy
- + monitoring the effective therapy regime
- + detection of drug/drug interactions
- + toxicity avoidance
- + monitoring of patient's compliance

### Please note:

The use of the RECIPE Kit System requires an LC system with tandem mass spectrometer (LC-MS/MS) with sufficient sensitivity and evaluation software.



### Clinical Background

**Benzodiazepines** are a group of psychoactive drugs with a broad range of therapeutic effects. They act as anxiolytics, sedatives and anticonvulsants and belong to the most frequently prescribed drugs all over the world. Currently around 50 different benzodiazepines are globally marketed. The chemical structure the drugs differ in pharmacokinetics and metabolic properties.

Long-term administration of benzodiazepines requires therapeutic drug monitoring (TDM).

**Therapeutic drug monitoring (TDM)** is the clinical laboratory practice to determine drug concentrations in blood to optimise a personalised pharmacotherapy, especially in indications with a small therapeutic range. Drug interactions, efficacy, toxicity avoidance and the surveillance of compliance are typical indications where TDM is requested.

**The RECIPE analytical method provides the reliable quantification of 35 different benzodiazepines.**

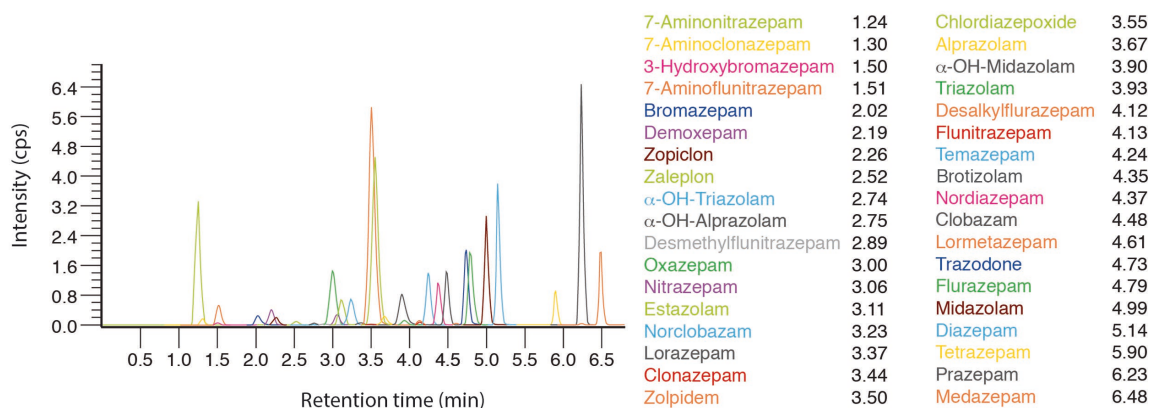


Figure 1 Chromatogram of the ClinCal® Serum Calibrator (order no. MS6013, level 2)



### Method Performance

The interassay precision of the method was determined with samples at two concentration levels. The samples were prepared by different persons on eight different days and measured on several systems from different manufacturers (for data from a specific system please contact [info@recipe.de](mailto:info@recipe.de)). The analyte concentrations were selected according to the respective therapeutic reference range and are contained in Table 2 together with the precision results.

| Analyte                | Concentration |          | Interassay Precision |          |
|------------------------|---------------|----------|----------------------|----------|
|                        | [µg/l]        |          | [%]                  |          |
|                        | Level I       | Level II | Level I              | Level II |
| 3-OH-Bromazepam        | 50            | 166      | 8.4                  | 7.2      |
| 7-Aminoclonazepam      | 15            | 50       | 3.8                  | 6.8      |
| 7-Aminoflunitrazepam   | 15            | 50       | 4.1                  | 5.7      |
| 7-Aminonitrazepam      | 60            | 200      | 4.9                  | 5.6      |
| α-OH-Alprazolam        | 15            | 50       | 8.6                  | 7.5      |
| α-OH-Midazolam         | 60            | 200      | 3.6                  | 3.5      |
| α-OH-Triazolam         | 12            | 40       | 5.9                  | 5.2      |
| Alprazolam             | 15            | 50       | 7.7                  | 6.5      |
| Bromazepam             | 90            | 300      | 6.0                  | 6.4      |
| Chlordiazepoxide       | 600           | 2000     | 2.8                  | 2.6      |
| Clobazam               | 150           | 500      | 4.7                  | 5.0      |
| Clonazepam             | 15            | 50       | 9.4                  | 8.5      |
| Demoxepam              | 600           | 2000     | 4.1                  | 5.4      |
| Desalkylflurazepam     | 30            | 100      | 7.8                  | 7.1      |
| Desmethylflunitrazepam | 15            | 50       | 3.9                  | 4.6      |
| Diazepam               | 300           | 1000     | 4.7                  | 6.4      |
| Estazolam              | 120           | 400      | 2.3                  | 6.2      |
| Flunitrazepam          | 15            | 50       | 4.7                  | 4.3      |
| Flurazepam             | 24            | 80       | 3.3                  | 4.3      |
| Lorazepam              | 60            | 200      | 5.3                  | 6.2      |
| Lormetazepam           | 6             | 20       | 5.7                  | 6.1      |
| Medazepam              | 120           | 400      | 4.5                  | 8.2      |
| Midazolam              | 90            | 300      | 5.4                  | 5.1      |
| Nitrazepam             | 60            | 200      | 6.6                  | 5.1      |
| Norclobazam            | 900           | 3000     | 2.9                  | 6.5      |
| Nordiazepam            | 240           | 800      | 3.0                  | 4.4      |
| Oxazepam               | 360           | 1200     | 3.1                  | 4.4      |
| Prazepam               | 240           | 800      | 5.8                  | 7.8      |
| Temazepam              | 120           | 400      | 5.6                  | 6.6      |
| Tetraazepam            | 120           | 400      | 8.3                  | 4.3      |
| Trazodone              | 480           | 1600     | 2.4                  | 8.3      |
| Triazolam              | 12            | 40       | 5.9                  | 6.3      |
| Zaleplon               | 24            | 80       | 4.2                  | 6.9      |
| Zolpidem               | 120           | 400      | 4.1                  | 4.8      |
| Zopiclone              | 24            | 80       | 12.4                 | 10.3     |

Table 2. Method Performance/Precision data



The following ranges are taken from the data collection according to Schulz et al.

| Analyt   | Therapeutic Range<br>[µg/l]  | Laboratory Alert Level <sup>†</sup><br>[µg/l] |
|--|--|---|
| 3-OH-Bromazepam  | n.a.   | n.a.  |
| 7-Aminoclonazepam  | n.a.   | n.a.  |
| 7-Aminoflunitrazepam                                       | n.a.   | n.a.  |
| 7-Aminonitrazepam  | n.a.   | n.a.  |
| α-OH-Alprazolam  | n.a.   | n.a.  |
| α-OH-Midazolam   | n.a.   | n.a.  |
| α-OH-Triazolam   | n.a.   | n.a.  |
| Alprazolam   | 5–50<br>20–40 (panic disorder)   | 100   |
| Bromazepam   | 50–200   | 300   |
| Chlordiazepoxide   | 400–3000   | 3500  |
| Clobazam   | 30–300   | 500   |
| Clonazepam   | Anticonvulsant: 20–70<br>Anxiolytic: 4–80  | Anticonvulsant: 80<br>Anxiolytic: 100         |
| Demoxepam  | *500–740   | *Toxic: 1000                                  |
| Desalkylflurazepam   | n.a.   | n.a.  |
| Desmethylflunitrazepam                                     | n.a.   | n.a.  |
| Diazepam plus<br>N-Desmethyldiazepam<br>(Nordiazepam)      | 100–2500   | 3000  |
| Estazolam  | *55–200  | n.a.  |
| Flunitrazepam  | 6–12 (sedation)<br>12–15 (sleep induction)   | 50  |
| Flurazepam<br>N-1-Desalkylflurazepam                       | 0–4 (at 1–3 h)<br>10–22 (at 1–3 h)<br>75–165 (at 10 h after drug<br>intake under steady state) | 330   |
| Lorazepam  | 30–100   | 300   |
| Lormetazepam   | 2–10 (at 1.5 h)  | 100   |
| Medazepam<br>desmethyldiazepam, temazepam<br>plus oxazepam | 200–2500   | 3000  |
| Midazolam  | 6–15<br>60–80 (at 1 h)   | 1000  |
| Nitrazepam   | 30–100 (at 0.5–2 h)  | 200   |
| Norclobazam (Desmethyloclobazam)                           | 300–3000   | 5000  |
| Nordiazepam<br>(Nordazepam)                                | 120–800  | 1500  |
| Oxazepam   | 200–1500   | 2000  |
| Prazepam   | *200–700   | *Toxic: 1000                                  |
| Temazepam  | 600–1100 (at 1 h)  | 2000  |
| Tetrazepam   | *50–600 (–1000)  | n.a.  |
| Trazodone  | 700–1000   | 1200  |
| Triazolam  | 2–20 (at 0.7–2 h)  | 40  |
| Zaleplon   | 20–40 (at 1–2 h)   | 200   |
| Zolpidem   | 80–160 (at 1–3 h)  | 320   |
| Zopiclone  | 55–85 (at 1.5–2 h)   | 300   |

\*Note:

e.g. 35–70 (20–50) means: Mainly a range between 35–70 mg/l is indicated, in some publications however a range between 20–50 mg/l

n.a.: not available



### Conclusion

#### The RECIPE 200 TDM Kit

- ✓ improves the individual therapeutic regimen for the patient
- ✓ adopts fast growing medical need by regular addition of new drug classes
- ✓ is validated, no new validation is necessary
- ✓ offers you a flexible expansion of the add-on sets



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