# DoseASSURE™

## OPTIMIZING RHEUMATIC DISEASE TREATMENT THROUGH BIOLOGICS

## *Dose*ASSURE™, LabCorp's portfolio of biologics monitoring assays, may help physicians optimize biological therapy using a personalized, patient-specific approach by:

- Aiding in titrating doses and adjusting frequency to maximize effectiveness[1,2]
- Identifying lack of response due to non-compliance or under-treatment[3]
- Assisting in preventing and managing loss of response due to immunogenicity[1,4]
- Predicting which patients are likely to retain long-term response[5]
- Minimizing cost to patient by avoiding unhelpful dose escalation[6]
- Avoiding overtreatment in low disease activity cases where tapering down is desirable[7]

| Biologic Drug Name | Primary Target | *Clinical Indications | Test Name | Test No. |
|---|---|---|---|---|
| **Adalimumab**<br>Humira® [AbbVie Biotechnology] | TNF | RA, JIA, PA, PP, AS, CD, UC | Adalimumab and Anti-Adalimumab Antibody (Serial Monitor), *Dose*ASSURE™ ADL | 503890 |
| **Certolizumab**<br>Cimzia® [UCB] | TNF | RA, PA, PP, AS, CD | Certolizumab and Anti-Certolizumab Antibody, *Dose*ASSURE™ CTZ | 504627 |
| **Etanercept**<br>Enbrel® [Immunex Corp.] | TNF | RA, JIA, PA, PP, AS | Etanercept and Anti-Etanercept Antibody (Serial Monitor), *Dose*ASSURE™ ETN | 504245 |
| **Golimumab**<br>Simponi® [Johnson & Johnson/Janssen Biotech, Inc.] | TNF | RA, PA, AS, UC | Golimumab and Anti-Golimumab Antibody, *Dose*ASSURE™ GOL | 504563 |
| **Infliximab**<br>Remicade® [Janssen Biotech, Inc.];<br>Inflectra® [Hospira UK, a subsidiary of Pfizer Inc]<br>Renflexis™ [Merck Sharp & Dohme Corp] | TNF | RA, PA, PP, AS, CD, UC** | Infliximab and Anti-Infliximab Antibody (Serial Monitor), *Dose*ASSURE™ IFX | 503870 |
| **Rituximab**<br>Rituxan® [Biogen MA Inc] | CD20 | RA, NHL, CLL | Rituximab and Anti-Rituximab Antibody, *Dose*ASSURE™ RTX | 504355 |
| **Ustekinumab**<br>Stelara® [Janssen Biotech, Inc.] | IL-12, IL-23 | CD, PA, PP | Ustekinumab and Anti-Ustekinumab Antibody, *Dose*ASSURE™ UST | 504594 |

* Partial listing of FDA-approved indications. TNF: tumor necrosis factor, CD: Crohn's Disease, UC: Ulcerative Colitis, RA: Rheumatoid Arthritis, PA: Psoriatic Arthritis, PP: Plaque Psoriasis, AS: Ankylosing Spondylitis, JIA: Juvenile Idiopathic Arthritis, NHL: Non-Hodgkin's Lymphoma, CLL: Chronic Lymphocytic Leukemia
** Published validation study, Marini JC, et al. Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade® AAPS Journal 2016. DOI: 10.1208/s12248-016-9981-3

## *Dose*ASSURE test porfolio provides both drug concentration (TDM) & anti-drug antibody (immunogenicity)

### Therapeutic Drug Monitoring (TDM)

- Biologics have variable pharmacokinetics.[2,4]
- Dosing by weight and empiric dose adjustment may be inefficient and suboptimal.[2,6]
- Clinical efficacy in RA and/or psoriasis has been shown to correspond with serum concentrations of infliximab, adalimumab, etanercept, golimumab, rituximab, and ustekinumab.[4,8-14]
- TDM for biologics is a valuable tool to evaluate doses and to tailor dose adjustments to your individual patient.[1-4,6]
- TDM can help differentiate non-compliance and under-treatment from other causes of lack of response.[3]
- Personalized treatment using TDM has been shown to improve both clinical and cost-effectiveness in RA.[6]

### Immunogenicity Testing (Anti-drug Antibody level)

- All biologics have the potential to induce an antibody-mediated immune response.[1,15]
- As many as one third of RA patients on biological therapy may develop anti-drug antibodies.[15,16]
- Anti-drug antibodies may appear as early as 2 weeks or as late as 3 years after the first infusion.[17]
- Co-therapy with methotrexate, sufficient drug levels, and maintenance dosing (vs. episodic or on-demand use) reduce the risk of anti-drug antibody formation.[15-20]
- Anti-drug antibodies can adversely affect the amount of drug in the body.[1,15,16,19] Therefore, concomitant measurement of anti-drug antibodies is an important adjunct to TDM for biologics.

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## Interpreting Drug Concentrations

- Higher drug trough levels have been correlated with clinical improvement as well as to higher rates of response and remission in rheumatic diseases[4,8-13]
- A consensus has yet to be reached about target ranges and maximally effective concentrations.[1]

**Optimal drug concentration depends on the disease and the desired therapeutic endpoint.**

## Interpreting Anti-Drug Antibody Levels

- Anti-drug antibodies may produce a range of effects with respect to the pharmacokinetics, efficacy, and cost-effectiveness of biologics.
- Low titer antibodies may have little or no effect on drug levels or clinical outcome. In fact, they may be transient and disappear over time, or they may progress to increasing titers.[1,16,18,21]
- In contrast, high titers of antibodies are likely to be more consequential, leading to loss of drug efficacy by preventing drug binding to TNF and/or increasing drug clearance.[1,16,19]

**Anti-drug antibody positivity should be interpreted in the context of the concomitant free drug level.**

| Drug | Normal half-life | Proposed Target Ranges for Trough Concentrations§ | Other clinical data on Trough Concentrations |
|---|---|---|---|
| Adalimumab | Approx. 2 weeks | 5 - 8 µg/mL in RA[9]; 5 - 8 µg/mL in PA[22]; 3.5 – 7.0 µ/mL in psoriasis[23] | |
| Certolizumab | Approx. 2 weeks | >23 µg/mL corresponded to better EULAR response rates.[24] | A definitive target range has yet to be determined. |
| Etanercept | 3 – 5.5 days | > 3.1 µg/mL (at 3 months predicted response at 6 months in RA.)[25] | In RA, good responders had higher levels (median 3.8 µg/mL 2.5 – 5.2) compared to non-responders (2.8 µg/mL 1.3 -3.9).[10] In AS, clinical responders (ASDAS) had higher median levels (median 3.8 µg/mL, 2.5 – 5.2) than non-responders (2.3 µg/mL, 1.2 – 3.4).[5] |
| Golimumab | Approx. 2 weeks | No consensus on clinical recommendation for RA | In RA, higher levels (median 3.4 µg/mL) were associated with a greater rate of clinical response (ACR20).[11] |
| Infliximab | 7.7 to 9.5 days | < 2 µg/mL: low and ≥ 8 µg/mL: high in RA[2] | In RA, responders had higher levels (median 3.6 µg/mL, 1.4 – 8.2) than non-responders (0.5 µg/mL, 0.2 – 2.2).[8] |
| Rituximab | 18 days (5.2-77.5 days) | No consensus on clinical recommendation for RA | |
| Ustekinumab | Approx. 3 weeks | A definitive target range has yet to be determined | In psoriasis, PASI 50 responders had higher trough concentrations than non-responders.[14] |

§Note: These targets concentrations were those used in landmark studies and do not necessarily translate into general recommendations for individual patients. Please see referenced literature for more details.

## When & where to collect blood on my patients?

- The **timing of sample collection** is important because the drug concentration will change during the dosing interval.
- The **trough concentration** (TC) is measured at the least variable time in the dosing interval, just before the next dose (same day to within < 7 days depending on the drug's normal half-life).
- During induction and maintenance phases, trough collections are usually recommended because target ranges are defined using TC.
- Blood can be drawn at any of **LabCorp's approximately1900 patient service centers** located nationwide.

### Additional RA and Treatment-Related Testing

| | | |
|---|---|---|
| 14.3.3 ETA/Rheumatoid Arthritis (504550) | Metabolic Panel (14), Comprehensive (322000) | Thiopurine Metabolites (503800) |
| C-Reactive Protein (CRP), Quantitative (006627) | Methotrexate Polyglutamates (504104) | Thiopurine Methyltransferase (TPMT), Enzyme Activity, Erythrocytes (510750) |
| Complete Blood Count With Differential (005009) | QuantiFERON®-TB Gold (182873) | Thiopurine Methyltransferase (TPMT) Genotyping (504142) |
| Cyclic Citrullinated Peptide (CCP) Antibodies, IgA, IgG, ELISA (164914) | Rheumatoid Arthritis (RA) Factor (006502) | Vectra® DA Disease Activity (819290) |
| Hepatitis B Virus (HBV) Evaluation Profile (037215) | Rheumatoid Arthritis (RA) Profile (164065) | |
| | Sedimentation Rate, Modified Westergren (005215) | |


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