

Biosimilar for natalizumab (Tyruko®) approved in Switzerland as of 01.06.2025

Statement of the Medico-Scientific Advisory Board of the Swiss MS Society

With the authorisation of Tyruko® (Sandoz), the first biosimilar to natalizumab (Tysabri®, Biogen), a significant step has been taken towards expanding access to highly effective therapies for relapsing forms of multiple sclerosis (MS). It contains the active ingredient natalizumab, a monoclonal antibody that specifically blocks the protein $\alpha 4\beta 1$ integrin on white blood cells and thus prevents them from entering the central nervous system. This significantly reduces inflammatory activity and thus the frequency of new flare-ups. Tyruko® is available as an infusion solution and is administered intravenously every four weeks like the original preparation Tysabri®. Tyruko® is not a generic, but a biosimilar - i.e. a copycat preparation that is very similar to the original in terms of structure, effect and safety, but not identical. Biosimilars must be tested again in studies before they are authorised, even if these are far less complex. Such studies show that Tyruko® is equivalent to the original preparation in terms of efficacy, safety and tolerability (1). The availability of Tyruko® provides a 30% more cost-effective alternative to Tysabri®.

At the same time, however, diagnostic problems arise, particularly when monitoring the risk of progressive multifocal leukoencephalopathy (PML), a rare but serious side effect in the form of infection of the brain with the JC virus (JCV). Patients with positive anti-JCV antibody tests and higher anti-JCV antibody concentrations in the blood have a significantly higher risk of developing PML than patients with negative anti-JCV antibody tests or low anti-JCV antibody concentrations. To date, Biogen's Stratify™ test has been used very successfully to precisely classify and stratify the risk of PML with Tysabri®.

The main diagnostic problem now is that Stratify™ (Biogen) is not available for monitoring Tyruko® (Sandoz) for licensing reasons and switching the anti-JCV antibody test from Stratify™ (Biogen) to ImmunoWELL™ (Sandoz) as part of Tyruko® therapy leads to inconsistent test results. Numerous studies from Germany, France, the United Kingdom and the Netherlands show that ImmunoWELL™ delivers false-positive results more frequently - especially in patients who have been considered JCV-negative for years under Stratify™ (2-5). In up to 47.6 % of cases, a JCV-seronegative patient (Stratify™) was classified as seropositive with ImmunoWELL™. Since, in contrast to the Stratify™ test, no reliable figures are available to date for the ImmunoWELL™ test to stratify the risk of PML with Tyruko®, this led to more intensive monitoring with more MRIs, additional visits to the doctor and potentially unnecessary treatment discontinuations or changes in treatment (in some cases back to Tysabri®), as well as uncertainty among patients and doctors about the actual risk of PML.

As ImmunoWELL™ has a high sensitivity but a low specificity and a low positive predictive value, the risk of PML is overestimated by this test and there is a danger of over-therapy, loss of treatment options or unnecessary worrying of patients.

The Scientific Advisory Board of the Swiss MS Society has compiled the following recommendations for practice based on a similar statement (6):

- 1) Despite the test discrepancies, Tyruko® can be used safely with correct management. An individualised risk-benefit assessment and clear explanation of test uncertainties to patients is important.
- 2) Patients with JCV-seronegative ImmunoWELL™ test who have not been pre-treated with Tysabri® have a very low risk of PML similar to patients with JCV-seronegative Stratify™ test and should receive standard monitoring as with Tysabri®.
- 3) Patients with JCV-seropositive ImmunoWELL™ test
 - a) who have not been pre-treated with Tysabri® can start therapy with Tyruko®, however
 - i) treatment should be limited to 12-24 months,
 - ii) risk mitigation measures should be evaluated (e.g. close MRI checks, possible extension of the dosing interval to 6 weeks - caution: limited evidence)
 - iii) and an adequate change in therapy should be planned early on;
 - b) or can perform a Stratify™ test (Biogen) and switch to Tysabri® if JCV test is negative.
- 4) Patients who switch from Tysabri® to Tyruko® and were JCV seronegative with Stratify™
 - a) and remain negative with ImmunoWELL™ can receive the usual monitoring.
 - b) and have a positive JCV sero-index with ImmunoWELL™
 - i) can start treatment with Tyruko®, however
 - treatment should be limited to 12-24 months,
 - risk mitigation measures should be evaluated (e.g. close MRI monitoring, possibly extending the dosing interval to 6 weeks - caution: limited evidence).
 - and an adequate change in therapy should be planned early (in the case of JCV sero-index values >1.4 better earlier);
 - ii) or can perform a Stratify™ test (Biogen) and should continue therapy with Tysabri® in the case of a JCV-negative Stratify™ test.
- 5) Patients with known JCV seropositivity and rising values under ImmunoWELL™ should receive increased monitoring and receive an adequate change in therapy as early as possible.

Desirable would be:

- Development and validation of new risk models based on ImmunoWELL™ data
- Independent, standardised JCV tests, decoupled from manufacturers' interests
- Joint efforts by clinicians, authorities, industry and patient associations to harmonise diagnostics

Important in all cases:

- Transparent communication with patients about test uncertainties
- Retention of MRI-based monitoring as a safety anchor

Overall, the introduction of Tyruko® is a step forward for MS therapy - but currently harbours diagnostic uncertainties due to test-related PML risk overestimates. Until a uniform, evidence-based testing strategy is established, careful, individualised management, transparent information and interdisciplinary collaboration (neurologists and test providers) are needed to treat patients safely and effectively.

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Literature

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3. Gelissen et al., JAMA Neurol 2025; 82(5): 523–525
4. Vukusic et al., Mult Scler 2025; 31(7): 877–881
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6. Dobson et al., Mult Scler Relat Disord. 2025; 22;100:106541