Saudi Public Assessment Report

Summary Report

Tysabri®

Type of Application: New Drug Application

Type of Product: Biological Drug

Active Pharmaceutical Ingredient(s): Natalizumab

ATC code: L04AA23

Dosage Form: Solution for subcutaneous injection in pre-filled syringe (PFS)

Dosage Strength: 150 mg/ml, 1 mL

Pack Size: 2 PFS

Shelf life: 24 Months

Storage Conditions: Store in a refrigerator, do not freeze.

Reference Product in SA (if applicable): NA

Marketing Authorization Holder: Biogen Netherlands B.V

Manufacturer: Vetter Pharma Fertigung GmbH & Co., Ravensburg, Germany.

Registration No.: 1905222045

Decision and Decision Date: Approved on 18/04/2022

Proposed Indications: Tysabri is indicated as a single disease modifying therapy in adults with highly active relapsing-remitting multiple sclerosis.

Product Background

The active drug substance in Tysabri is Natalizumab, which is a recombinant, humanized, anti-α4 integrin antibody that is produced in a murine cell line. Natalizumab gives its biological activity via a selective adhesion-molecule inhibitory and binding to the α4 subunit of human integrin, which is highly expressed on the surface of all leukocytes, except for neutrophils. Specifically the α4β1 integrin and blocking the interaction with its cognate receptor, VCAM-1, and ligands, osteopontin, and an alternatively spliced domain of fibronectin connecting segment 1, and also blocks the interaction of α4β7 integrin with the mucosal addressing cell adhesion molecule 1. Disruption of these molecular interactions prevents the transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells.

Tysabri is indicated as a single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active diseases despite a full and adequate course of treatment with at least one disease modifying therapy.
- Or patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain Magnetic Resonance Imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

The SFDA approval for Tysabri® (Natalizumab) is based on a review of the quality, safety and efficacy as summarized hereinafter:

Quality Aspects

Tysabri 150 mg is a colorless to slightly yellow, slightly opalescent to opalescent solution formulated with Sodium phosphate, monobasic, monohydrate, dibasic, heptahydrate Sodium chloride and Polysorbate 80 presented in a prefilled syringe. The quality assessment for this medicine undertaken to meet the last version of *GCC Data Requirements for Human Drugs Submission.* Tysabri is previously approved by SFDA as 300 mg natalizumab in 15 ml glass vials for intravenous infusion. For patient convenience, the applicant seeks approval for an additional route of administration, subcutaneous injection. The subcutaneous presentation will also be used to administer 300 mg of natalizumab and will be supplied as two 150 mg/ml pre-filled syringes, each containing 1 ml. The submitted quality information included the manufacturing process development, comparability, SC, the drug substance manufacturing steps for the subcutaneous (SC) formulation are identical to the natalizumab intravenous (IV) drug substance manufacturing steps from cell culture through the end of the ultrafiltration step. An additional ultrafiltration step

is used to further concentrate the drug substance to 150 mg/ml to enable a subcutaneous dose, the manufacturing processes for both drug substance and drug product are described with sufficient detail, according to the control and validation for all critical steps that may affect the critical quality attributes .There are no issues pertaining to drug substance and drug product specification and stability analytical procedures are validated, since it's complied with the relevant guidelines.

Clinical Aspects

The clinical development program for Tysabri consisted of two pivotal efficacy and safety clinical studies: C-1801 and C-1802, and one phase II tolerability and efficacy study (101MS206).

Summary of the clinical studies presented hereafter:

- C-1801 study: A phase III randomized, double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety and efficacy of natalizumab in 942 adult subjects (aged between 18-50) with relapsing-remitting multiple sclerosis. The primary objective of the study was to determine the efficacy of natalizumab in reducing the rate of clinical relapses at one year and slowing the progression of disability at two years, as measured by at least a 1.0 point increase on the Expanded Disability Status Scale (EDSS).

- C-1802 study: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to determine the safety and efficacy of natalizumab when added to Avonex® (interferon beta-1a) in 1171 adult subjects (aged between 18-55) with relapsing-remitting multiple sclerosis. The primary objective of the study was to determine whether adding natalizumab to the standard regimen of Avonex in comparison to placebo addition, was effective in reducing the rate of clinical relapses at one year, and to determine whether adding natalizumab to the standard regimen of Avonex in comparison to placebo addition, was effective in slowing the progression of disability at two years, as measured by at least a 1.0 point increase on the Expanded Disability Status Scale (EDSS).

- 101MS206 study: A randomized, single-blinded, parallel-group, phase 2 study explores the safety, tolerability, and efficacy of multiple regimens of natalizumab in adult subjects (aged between 18-55) with relapsing-multiple sclerosis. The study aimed to explore the effects of multiple regimens of natalizumab on disease activity and safety in 291 subjects with relapsing-remitting multiple sclerosis. The primary outcome of the study was the cumulative number of combined unique active lesions based on brain magnetic resonance imaging (MRI) scans up to Week 60.

The pharmacokinetics, efficacy and safety results from the aformentioned studies were fully assessed by the SFDA efficacy and safety department. Based on a comprehensive review of the

submitted evidence, the benefit/risk balance of Tysabri is considered favorable. Therefore, we recommend the approval of the marketing authorization of Tysabri.

Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published at (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa