Sandoz International
Sandoz Global Communications
Lichtstrasse 35
4056
Basel

https://www.sandoz.com

MEDIA & INVESTOR RELEASE

Sandoz Supplemental Biologics License Application accepted by US FDA for biosimilar Hyrimoz® (adalimumab-adaz) high concentration formulation (HCF)

- *Submission supported by comprehensive analytical data package and clinical Phase I pharmacokinetics bridging study*
- *Proposed Hyrimoz® HCF would help expand access to medicine for patients with chronic immune-mediated inflammatory diseases*
- *Sandoz is committed to supporting healthcare professionals to advance patient care and improve access to medicines sustainably and affordably*

Basel, July 21, 2022 – Sandoz, a global leader in generic and biosimilar medicines, today announced that the US Food and Drug Administration (FDA) has accepted for review its Supplemental Biologics License Application (sBLA) for a high concentration formulation of 100 mg/mL (HCF) of its biosimilar Hyrimoz® (adalimumab-adaz). The application includes the indications of the reference medicine Humira® (adalimumab)* not protected by orphan exclusivity, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

"Biosimilars play a crucial role in generating billions of dollars of savings for patients and the US healthcare system every year, while improving healthcare sustainability," said Keren Haruvi, President, Sandoz Inc., Head of North America. "Should the Hyrimoz HCF be approved, we believe this important biosimilar medicine would help expand access to more patients with serious inflammatory diseases, including those who currently may not have access to it."

Hyrimoz 50 mg/mL was approved by the US FDA in 2018. In accordance with recommendations from the US FDA, Sandoz conducted a Phase I pharmacokinetics (PK) bridging study comparing Hyrimoz 50 mg/mL and citrate-free Hyrimoz HCF. This study met all of the primary objectives, demonstrating comparable pharmacokinetics and showing similar safety and immunogenicity of the Hyrimoz 50 mg/mL and Hyrimoz HCF.

Recently, the European Medicines Agency also accepted the application for Sandoz proposed Hyrimoz HCF.

The potential US FDA approval of the HCF for Hyrimoz builds on the already approved and well-established Sandoz global biosimilar portfolio in immunology. Sandoz has more than 65 million days of patient experience with Hyrimoz 50 mg/mL worldwide and if approved, Hyrimoz

100 mg/mL citrate-free HCF would represent the first launch of a Sandoz biosimilar in the US market in this specific disease space.

Sandoz is committed to helping millions of patients access biologic medicines sustainably in areas including oncology and immunology. With a strong global portfolio of eight marketed biosimilars and a further 15+ in various stages of development, Sandoz has an unparalleled heritage and extensive expertise in the development, manufacturing and delivery of biosimilar medicines to patients and the healthcare community worldwide.

About adalimumab
Adalimumab is a human immunoglobulin G1 (IgG(1)) monoclonal antibody targeting tumor necrosis factor alpha (TNF-a). The adalimumab reference medicine (Humira®) was first approved with an adalimumab concentration of 50 mg/mL .[1,2] In 2015, the US FDA and European Medicines Agency approved Humira® HCF, which contains adalimumab at a concentration of 100 mg/mL.[3,4]

Important Safety Information

INDICATIONS:
HYRIMOZ is a tumor necrosis factor (TNF)-blocker indicated for:

- **Rheumatoid Arthritis (RA):** reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA):** reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- **Psoriatic Arthritis (PsA):** reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS):** reducing signs and symptoms in adult patients with active AS.
- **Crohn's Disease (CD):** treatment of moderately to severely active Crohn's Disease in adult patients.
- **Ulcerative Colitis (UC):** treatment of moderately to severely active ulcerative colitis in adult patients.
  Limitations of use: effectiveness has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (Ps):** treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

IMPORTANT SAFETY INFORMATION:

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with adalimumab products, including HYRIMOZ, are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue HYRIMOZ if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB. Patients with TB have frequently presented with disseminated or extrapulmonary disease. Test patients for latent TB before HYRIMOZ use and during therapy. Initiate treatment for latent TB prior to HYRIMOZ use.**

- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Carefully consider the risks and benefits of treatment with HYRIMOZ prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with HYRIMOZ, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers including adalimumab products. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF-blockers including adalimumab products. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF-blocker cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6-mercaptopurine (6–MP) concomitantly with a TNF-blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF-blocker or a TNF-blocker in combination with these other immunosuppressants.

WARNINGS AND PRECAUTIONS

Serious Infections

- Do not start HYRIMOZ during an active infection, including localized infections.
- If an infection develops, monitor carefully, and stop HYRIMOZ if infection becomes serious. Drug interactions with biologic products: A higher rate of serious infections has been observed in RA patients treated with rituximab who received subsequent treatment with a TNF blocker. An increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no demonstrated added benefit in patients with RA. Concomitant administration of HUMIRA with other biologic DMARDs (e.g., anakinra or abatacept) or other TNF blockers is not recommended based on the possible increased risk for infections and other potential pharmacological interactions.
- Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants, may be at greater risk of infection.
- *Invasive fungal infections:* For patients who develop a systemic illness on HYRIMOZ, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic.

Malignancies

- In clinical trials, incidence of malignancies was greater in adalimumab -treated patients than in controls.
- Consider the risks and benefits of TNF-blocker-treatment, including HYRIMOZ, prior to initiating therapy in patients with known malignancy.

- Non-Melanoma Skin Cancer (NMSC) was reported during clinical trials for adalimumab-treated patients. Examine all patients, particularly those with a history of prolonged immunosuppressant or PUVA therapy for the presence of NMSC prior to and during treatment with HYRIMOZ.
- In the adalimumab clinical trials there was an approximate 3-fold higher rate of lymphoma than expected in the general U.S. population. Patients with chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk than the general population for the development of lymphoma, even in the absence of TNF-blockers.
- Post-marketing cases of acute and chronic leukemia have been reported in association with TNF-blocker use. Approximately half of the post-marketing cases of malignancies in children, adolescents, and young adults receiving TNF blockers were lymphomas; other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents.

Hypersensitivity Reactions

- Anaphylaxis or serious allergic reactions have been reported following administration of adalimumab products. If an anaphylactic or other serious allergic reaction occurs, immediately discontinue administration of HYRIMOZ and institute appropriate therapy.

Hepatitis B Virus Reactivation

- Use of TNF-blockers, including HYRIMOZ, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases have been fatal.
- Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating TNF-blocker therapy.
- Exercise caution in patients identified as carriers of HBV and closely monitor during and after Hyrimoz treatment.
- In patients who develop HBV reactivation, stop HYRIMOZ and initiate effective anti-viral therapy. Exercise caution when resuming HYRIMOZ after HBV treatment.

Neurologic Reactions

- Use of TNF-blocking agents, including adalimumab products, has been associated with rare cases of new onset or exacerbation of central nervous system and peripheral demyelinating disease, including multiple sclerosis (MS), optic neuritis, and Guillain-Barré syndrome.
- Exercise caution when considering HYRIMOZ for patients with these disorders; discontinuation of Hyrimoz should be considered if any of these disorders develop.

Hematological Reactions

- Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF-blocking agents. Medically significant cytopenia has been infrequently reported with adalimumab products.
- Consider stopping HYRIMOZ if significant hematologic abnormalities occur.

Heart Failure

- Worsening and new onset congestive heart failure (CHF) has been reported with TNF-blockers. Cases of worsening CHF have also been observed with adalimumab products; exercise caution and monitor carefully.

Autoimmunity

- Treatment with adalimumab products may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. Discontinue treatment if symptoms of a lupus-like syndrome develop.

Immunizations

- Patients on HYRIMOZ should not receive live vaccines.
- Pediatric patients, if possible, should be brought up to date with all immunizations prior to initiating HYRIMOZ therapy.
- Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant. The safety of administering live or live-attenuated vaccines in infants exposed to

adalimumab products *in utero* is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

ADVERSE REACTIONS
The most common adverse reactions (incidence > 10 %): infections (e.g., upper respiratory, sinusitis), injection site reactions, headache and rash.

Please see full Prescribing Information for Hyrimoz.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Disclaimer
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About Sandoz
Sandoz, a Novartis division, is a global leader in generic pharmaceuticals and biosimilars. Our purpose is to pioneer access for patients by developing and commercializing novel, affordable approaches that address unmet medical needs. Our ambition is to be the world’s leading and most valued generics company. Our broad portfolio of high-quality medicines, covering all major therapeutic areas, accounted for 2021 sales of USD 9.6 billion.

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Instagram: https://www.instagram.com/sandozglobal

CEO Richard Saynor on LinkedIn: https://www.linkedin.com/in/richard-saynor/

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*Humira is a registered trademark of AbbVie Biotechnology Ltd

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Sandoz Global Communications
Chris Lewis
Sandoz Global
Communications
+49 174 244 9501 (mobile)
chris.lewis@sandoz.com

Sandoz US Communications
Leslie Pott
Sandoz US Communications
+1 201 354 0279 (mobile)
leslie.pott@sandoz.com

Novartis Media Relations
E-mail: media.relations@novartis.com

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 778 5052
Nicole Zinsli-Somm	+41 79 325 2084		
Isabella Zinck	+41 61 324 7188		