

UNIVERSITA' DEGLI STUDI DI VERONA

DIPARTIMENTO DI

MEDICINA

SCUOLA DI DOTTORATO DI

SCIENZE DELLA VITA E DELLA SALUTE

DOTTORATO DI RICERCA IN

SCIENZE BIOMEDICHE CLINICHE E SPERIMENTALI

37° CICLO/ ANNO 2021-2022

**PRICE VARIABILITY OF TNF- α INHIBITOR BIOSIMILARS
ACROSS EUROPEAN COUNTRIES**

S.S.D. MED/35

Coordinatore: Prof. Davide Gatti

Tutor: Prof. Paolo Gisondi

Dottorando: Dott. Davide Geat

Price variability of TNF- α inhibitor biosimilars across European countries

Davide Geat

Tesi di Dottorato

Verona, 2 Dicembre 2024

ABSTRACT

Background: The price of TNF- α inhibitor biosimilars of adalimumab, etanercept and infliximab is lower than their respective originators, but their price variability in Europe has not been investigated yet.

Objectives: The aim of this study was to investigate the price variability of TNF- α inhibitor biosimilars across European countries.

Methods: A survey was conducted among five dermatologists working in academic reference centres for psoriasis in Denmark, France, Germany, Italy and Spain. The survey assessed the pharmacy price of one package of adalimumab, etanercept and infliximab biosimilars and their originators as well as the price per unit dose (i.e. the amount of medication administered to a patient in a single dose) paid by local hospital pharmacies.

Results: The highest biosimilar prices were reported in Germany and the lowest ones in Italy and Spain, with prices in France and Denmark lying in between. In particular, regarding adalimumab biosimilars, the highest price per unit dose was reported in Germany (€494.51) while the lowest one in Spain (€21.00). Regarding etanercept biosimilars, the highest price per unit dose was also reported in Germany (€282.52) while the lowest one in Italy (€11.69). Lastly, regarding infliximab biosimilars, the highest price per unit dose was reported in Germany (€716.45) while the lowest one in Spain (€191.60).

Conclusion: Considerable differences were found in the price of TNF- α inhibitor biosimilars across European countries. Such biosimilar price variability may have a strong impact on healthcare costs and influence psoriasis patients' access to biological treatment.

INDEX

Abstract.....	3
Introduction.....	9
Epidemiology of psoriasis.....	9
Pathogenesis.....	9
Clinical presentation.....	11
Disease assessment.....	14
Treatment.....	16
Biosimilars in psoriasis.....	28
Biosimilar utilization for psoriasis in Europe.....	34
Biosimilar regulatory framework and pricing policies in Europe.....	34
Comorbidities.....	39
Economic burden.....	44
Aim of the study.....	48
Materials and methods.....	48
Results.....	49
Discussion.....	63
Conclusion.....	68
References.....	69
Supplementary files.....	85

LIST OF TABLES

Table 1. Psoriasis Area and Severity Index (PASI).....	15
Table 2. Dermatology Life Quality Index (DLQI) domains.....	16
Table 3. Conventional systemic treatments used for chronic plaque psoriasis ...	18
Table 4. TNF- α inhibitors approved for chronic plaque psoriasis.....	21
Table 5. IL-17 inhibitors approved for chronic plaque psoriasis.....	23
Table 6. IL-12/23 and IL-23 inhibitors approved for chronic plaque psoriasis...	25
Table 7. Oral small molecules approved for chronic plaque psoriasis.....	27
Table 8. Currently available biosimilars approved in the European Union for chronic plaque psoriasis.....	29
Table 9. List of the most common diseases associated with plaque psoriasis.....	40
Table 10. CASPAR (Classification for Psoriatic Arthritis) criteria.....	41
Table 11. Costs of psoriasis per patient per year in the five largest European countries and in the United States.....	45
Table 12. Economic burden of the comorbidities associated with psoriasis.....	47
Table 13a. Drug price per unit dose of adalimumab originator before loss of exclusivity and of the originator and its biosimilars in 2024.....	53

Table 13b. Percentual discount of the price of a unit dose of adalimumab originator and its biosimilars in 2024 compared to the originator price before loss of exclusivity 53

Table 13c. Monthly maintenance regimen cost (steady state) of adalimumab originator before loss of exclusivity and with the originator and its biosimilars in 2024.....54

Table 13d. Annual cost of treatment (including induction) of adalimumab originator before loss of exclusivity and with the originator and its biosimilars in 2024.....54

Table 13e. Price per milligram (mg) of adalimumab originator before loss of exclusivity and with the originator and its biosimilars in 2024.....55

Table 14a. Drug price per unit dose of etanercept originator before loss of exclusivity and of the originator and its biosimilars in 2024.....56

Table 14b. Percentual discount of the price of a unit dose of etanercept originator and its biosimilars in 2024 compared to the originator price before loss of exclusivity.....57

Table 14c Monthly maintenance regimen cost (steady state) of etanercept originator before loss of exclusivity and with the originator and its biosimilars in 2024.....57

Table 14d. Annual cost of treatment (including induction) of etanercept originator before loss of exclusivity and with the originator and its biosimilars in 2024.....58

Table 14e. Price per milligram (mg) of etanercept originator before loss of exclusivity and with the originator and its biosimilars in 2024.....58

Table 15a. Drug price per unit dose of infliximab originator before loss of exclusivity and of the originator and its biosimilars in 2024.....60

Table 15b. Percentual discount of the price of a unit dose of infliximab originator and its biosimilars in 2024 compared to the originator price before loss of exclusivity.....60

Table 15c. Monthly maintenance regimen cost (steady state) of infliximab originator before loss of exclusivity and of the originator and its in 2024.....61

Table 15d. Annual cost of treatment (including induction) of infliximab originator before loss of exclusivity and with the originator and its biosimilars in 2024.....61

Table 15e. Price per milligram (mg) of infliximab originator before loss of exclusivity and with the originator and its biosimilars in 2024.....62

LIST OF FIGURES

Figure 1. Drug price per unit dose of adalimumab originator before loss of exclusivity and of the originator and its biosimilars in 2024.....55

Figure 2. Percentual discount of the price of a unit dose of adalimumab originator and its biosimilars in 2024 compared to the originator price before loss of exclusivity.....56

Figure 3. Drug price per unit dose of etanercept originator before loss of exclusivity and of the originator and its biosimilars in 2024.....59

Figure 4. Percentual discount of the price of a unit dose of etanercept originator and its biosimilars in 2024 compared to the originator price before loss of exclusivity.....59

Figure 5. Drug price per unit dose of infliximab originator before loss of exclusivity and of the originator and its biosimilars in 2024.....62

Figure 6. Percentual discount of the price of a unit dose of infliximab originator and its biosimilars in 2024 compared to the originator price before loss of exclusivity.....63

INTRODUCTION

Epidemiology of psoriasis

Psoriasis is a chronic immune-mediated cutaneous disease that affects 2-3% of the population worldwide [1], which corresponds to about 125 million people [2]. Its prevalence is higher in countries with high income and older populations [3]. The age of onset of psoriasis presents a bimodal distribution, peaking in men at 30–39 years and 60–69 years while approximately 10 years earlier in women [3]. However, the disease may first commence at any age from infancy (such as napkin psoriasis) to old age. Based on the age of onset, psoriasis can be classified as early-onset psoriasis (or type 1 psoriasis) which starts before 40 years old, and late-onset psoriasis (or type 2 psoriasis) whose onset is after 40 years old [4]. Type 1 psoriasis accounts for more than 75% of all psoriasis cases and, compared with type 2 psoriasis, is more commonly associated with a positive family history of psoriasis (siblings of type 1 psoriasis patients have a three-fold risk to develop psoriasis) and human leucocyte antigen (HLA)-Cw6 [4].

Pathogenesis

The pathogenesis of psoriasis is multifactorial and is characterized by several genetic as well as environmental contributors [2]. Genetic factors are particularly important for early-onset psoriasis as shown by twin, family-based and large-scale population-level studies, which estimated the heritability of psoriasis to range from 60 to 90% [5]. Genome-wide association studies (GWAS) have identified more than 60 susceptibility loci which are related to both the skin barrier function (LCE3) and the immune system function, such as interleukin (IL)-23/Th17 axis (IL23R, IL12B and TYK2), antigen presentation (HLA-C, ERAP1), NF-κB signaling (TNIP1) and type 1 INF (interferon) pathway (RNF113 and IFIH1) [6]. The major susceptibility locus for psoriasis, named PSORS1, is located at 6p21, and was found to be overrepresented in all psoriatic populations analyzed [7-12]. Of note, there are several other loci which have been associated with psoriasis including those on chromosomes 1p (PSORS7), 14 1q (PSORS4), 16 3q (PSORS5), 17 4q (PSORS3), 18 17q (PSORS2), 19 and 19p (PSORS6) [13-17].

However, unlike PSORS1, the strength of the association between those latter genes and susceptibility to psoriasis is variable, which may at least in part explained by the genetic heterogeneity of the different psoriatic patients analyzed across different countries [4]. Interestingly, pustular psoriasis (a less common variant of psoriasis) was found to be genetically distinct from plaque psoriasis and is associated with different susceptibility genes such as IL36RN, AP1S3 and CARD14 [18].

Furthermore, several environmental factors are at play in the pathogenesis of psoriasis. First, drugs such as lithium, interferon, antimalarials (i.e. hydroxychloroquine) and certain beta-blockers (i.e. practolol) are known to represent triggers of psoriasis [4]. Also, the rapid withdrawn of steroids or other immunosuppressants may result in a rebound exacerbation of psoriasis and in the induction of a severe form of psoriasis, namely acute generalized pustular psoriasis. Secondly, alcohol and smoking have been associated with the induction and worsening of psoriasis, with smoking being strongly associated with localized pustular psoriasis of the palms and the soles [4]. Furthermore, infections can represent a trigger for psoriasis. Streptococcal infection, particularly of the throat, is a well-established trigger for guttate psoriasis. Moreover, human immunodeficiency virus (HIV) infection is associated with psoriasis, with these patients having a threefold risk of developing psoriasis. Furthermore, psoriasis can develop in the sites of previous trauma, an effect known as the Koebner phenomenon. Traumas which can trigger psoriasis include scratch marks, surgical incisions, tattoos, sunburns and irritants (such as in the case of napkin psoriasis in infants). Furthermore, pregnancy – while associated in most patients with an amelioration of psoriasis – can rarely exacerbate the disease and even lead to the development of generalized pustular psoriasis. Furthermore, hypocalcemia (i.e. secondary to parathyroidectomy or during dialysis) may precipitate psoriasis. Lastly, stress and obesity have been associated with the induction and/or exacerbation of psoriasis [2,6,19].

From an immunological perspective, the pathogenesis of psoriasis is complex, and involves the excessive proliferation and abnormal differentiation of keratinocytes and the infiltration of multiple inflammatory cells in the skin. This stems from the

interplay between keratinocytes, T cells, dendritic cells, and other skin-resident cells, with the IL-23/Th17 axis being the central driver of immune activation, chronic inflammation and keratinocyte proliferation [6,20,21]. In particular, activated plasmacytoid dendritic cells (pDCs) trigger myeloid dendritic cells (mDCs) maturation and production of TNF- α , IL-12, and IL-23. These cytokines, in turn, promote the activation of T helper 1 (Th1) and Th17 which fuel inflammation by producing inflammatory cytokines such as TNF- α , IL-17, IL-21 and IL-22 [6,20]. Furthermore, these cytokines (particularly IL-17) activate keratinocyte to proliferate and produce antimicrobial peptides, cytokines, and chemokines, which also contribute to psoriatic inflammation [6,20]. Cytokines are fundamental in the pathogenesis of psoriasis and, among those, TNF- α , IL-17A, and IL-23 are of crucial importance in psoriasis as they represent targets of biologic agents used to treat psoriasis [6,20]. Of note, while the role of immune cells has historically been underscored in psoriasis, cytokines derived from keratinocytes have also recently gained attention. Indeed, keratinocytes are critical cytokine responders in the pathogenesis of psoriasis and have an important role in the initiation and maintenance of psoriasis [21]. This was shown by psoriatic mouse models in which keratinocyte-specific deletion of receptors such as IL-17RA and IL-36R led to the amelioration of psoriasiform lesions [21]. Importantly, several factors other than cytokines (such as transcription factors, non-coding RNAs, antimicrobial peptides and metabolism) may modulate keratinocyte functioning and could represent targets for future therapies in psoriasis [21].

Clinical presentation

From a clinical point of view, psoriasis can be classified as chronic plaque psoriasis (the most commonly encountered variant), sebopsoriasis (an overlap between seborrheic dermatitis and psoriasis), guttate psoriasis, pustular psoriasis and erythrodermic psoriasis [6]. Other less common variants include follicular psoriasis and rupioid psoriasis. Based on its localization, it can be further classified as diffuse psoriasis, scalp psoriasis, inverse (or flexural) psoriasis, facial psoriasis, genital psoriasis, nail psoriasis and napkin psoriasis [6].

The most common form is chronic plaque psoriasis, which is characterized by symmetrical, well-defined and slightly raised salmon-pink plaques covered by silvery-white scales. The lesions are generally asymptomatic although itching can sometimes be present. When the scale is scraped away, psoriatic plaques reveal tiny bleeding points from the dilated superficial capillaries, something known as the Auspitz sign [6]. Occasionally, a clear halo surrounding the plaques can be observed, and is named Woronoff ring. The size and shape of the plaques varies greatly and smaller plaques can coalesce into larger plaques. Furthermore, annular configurations might (albeit less commonly) be observed due to the healing starting in the central portion of the plaques. The localization of chronic plaque psoriasis is characteristic and is a crucial factor in the differential diagnosis between psoriasis and other inflammatory cutaneous diseases such as eczema. It most commonly affects the extensor surfaces (especially elbows and knees), sacrum and scalp [6]. Other areas may also be involved such as the genitalia and the face, the latter being more commonly in pediatric forms.

Inverse (or flexural psoriasis) is characterized by erythematous plaques with minimal or absent desquamation located on the axillae, sub-mammary folds, inguinal folds and intergluteal cleft [6]. While infective intertrigo (mycotic or bacterial) may share similarities with inverse psoriasis as both present with erythematous plaques located on flexural areas, the chronic nature of psoriasis and its symmetrical and well-demarcated lesions suggest the diagnosis of inverse psoriasis.

Guttate psoriasis is characterized by the acute onset of numerous small drop-like (“guttate”) papules and plaques located on the trunk and limbs, sparing the face, palms and soles [6]. It is commonly observed in adolescents and young adults and typically starts 3-4 weeks after a streptococcal throat infection. Notably, 40% of patients with guttate psoriasis may develop chronic plaque psoriasis in later years. Several acute inflammatory cutaneous diseases should be differentiated from guttate psoriasis, including pityriasis rosea (which is not preceded by a streptococcal infection and whose eruption is preceded by the appearance of a herald patch) and secondary syphilis (which is associated with palmoplantar lesions, lymphadenopathy and mucosal lesions).

Erythrodermic psoriasis is characterized by a widespread erythematous eruption (erythroderma) which may be scaly (exfoliative) [6]. Temporary hair loss and nail alterations (i.e. horizontal ridging, nail shedding) can be present. It can be also associated with systemic features such as fever, leukocytosis. Generalized vasodilation can lead to hypothermia due to increased body heat loss while the increased cutaneous blood flow induces a rapid increase in cardiac output which can trigger high-output heart failure, particularly in patients with pre-existing cardiac disease. Furthermore, erythrodermic psoriasis results in impaired skin barrier function with increased percutaneous water loss. This can, in turn, lead to dehydration and acute kidney failure. Also, impairment of the skin barrier predisposes to infections, while increased cutaneous protein and iron loss may lead to hypoproteinemia and iron deficiency anemia. Erythrodermic psoriasis can be induced by drugs, infections and hypocalcemia. Of note, other conditions which can induce erythroderma - such as eczema, mycosis fungoides, Sezary syndrome, pityriasis rubra pilaris and drug eruptions - should be differentiated and a skin biopsy is therefore always needed.

Pustular psoriasis is a rarer variant of psoriasis which includes acute generalized pustular psoriasis, acrodermatitis continua of Hallopeau, palmoplantar pustulosis, pustular psoriasis of pregnancy, and infantile and juvenile pustular psoriasis. Pustular psoriasis is characterized by the presence of sterile pustules on an erythematous base which histologically corresponds to a sterile neutrophilic infiltrate [6]. Its most severe form, acute generalized pustular psoriasis, is characterized by confluent sheets of tiny pustules on a background of erythroderma which form lakes of pus and circinate configurations and exfoliate as they heal. The lesions are located on non-acral sites. The condition is associated with systemic involvement including fever, erythrocyte sedimentation rate (ESR) elevation, leukocytosis. Complications such as sepsis, cardiac failure, hypovolemia, acute kidney failure and liver damage may ensue. This form of psoriasis can be induced by drugs, hypocalcemia, stress, Koebner phenomenon (irritating topical products, sunburns). Importantly, the abrupt discontinuation of systemic steroids may also induce acute generalized pustular psoriasis.

In acrodermatitis continua of Hallopeau, sterile pustules coalescing into pus lakes and associated with erythema and desquamation appear on a digit (fingers or, less commonly, toes). The lesions can be painful and have a recalcitrant course. Nail dystrophy and rarely bone osteolysis may ultimately develop. This condition is more common in females and carries a risk of progression to generalized pustular psoriasis.

Palmo-plantar pustulosis is characterized by yellow pustules on a background of erythema and desquamation, symmetrically located on the palms and/or soles. The condition is encountered more frequently in post-menopausal women and is associated with cigarette smoking.

Nail alterations are found in about one third of psoriatic patients, but may also be the only manifestation of psoriasis [6]. Psoriatic nail alterations include pitting (nail indentations due to parakeratosis), onycholysis (separation of nail plate from nail bed), oil spots (discoloration of the nailbed), splinter hemorrhages, nail dystrophy and subungual hyperkeratosis. Importantly, nail psoriasis is associated with an increased risk of developing psoriatic arthritis due to the anatomical vicinity between nail matrix and entheses. Indeed, psoriatic nail dystrophy represents one of the CASPAR (CLASSification criteria for Psoriatic Arthritis) criteria for the diagnosis of psoriatic arthritis.

Disease assessment

The most commonly used tools to assess psoriasis severity and treatment response are body surface area (BSA), Physician Global Assessment (PGA) and PASI (Psoriasis Area and Severity Index) [22].

PGA is a global assessment of all lesions scored on a scale from 0 to 5, with 0 representing clear skin, 1 almost clear skin, and 5 representing severe psoriasis [22]. PASI evaluates the percentage of skin involvement in four body areas (head, arms, trunk and legs) using grades from 0 to 6, and the severity of erythema, induration and desquamation in each area using a scale from 0 to 4 (Table 1). The sum of severity parameters is then calculated for each section of skin, multiplied by the area score for each area and by the weight of the respective section (0.1 for head, 0.2 for arms, 0.3 for trunk and 0.4 for legs) [22].

Table 1. Psoriasis Area and Severity Index (PASI).

E = erythema; I = induration; D = desquamation 0 = complete lack of 1 = slight 2 = moderate 3 = severe 4 = severest possible
A = percentage of surface area involved 0 = no psoriasis 1 = < 10% 2 = 10<30% 3 = 30<50% 4 = 50<70% 5 = 70<90% 6 = 90-100%
PASI = 0.1(E_h + I_h + D_h)A_h + 0.3(E_t + I_t + D_t)A_t + 0.2(E_u + I_u + D_u)A_u + 0.4(E_l + I_l + D_l)A_l <i>where: h = head; t = trunk; u = upper extremities; l = lower extremities</i>

When assessing treatment response, PASI75, PASI90 and PASI100 are used to indicate a 75/90/100% or greater reduction in PASI scores from baseline. Lastly, the Dermatology Life Quality Index (DLQI) is ten-question questionnaire used to measure the impact of skin disease on the quality of life across six domains (Table 2) and is also commonly used to assess the impact of psoriasis on the quality of life [23]. The DLQI describes the overall impact of skin disease on a person's health-related quality of life as follows: 0-1 no effect; 2-5 small effect; 6-10 moderate effect; 11-20 very large effect; 21-30 extremely large effect. Whilst there appears to be no correlation or only weak correlation between PASI and DLQI scores, there is a correlation between an improvement in PASI and an improvement in DLQI [24,25].

Table 2. Dermatology Life Quality Index (DLQI) domains.

Domain	Score
Symptoms and feelings	0-6
Daily activities	0-6
Leisure	0-6
Work and school	0-3
Personal relationships	0-6
Treatment	0-3
Total	0-30

Treatment

The treatment of chronic plaque psoriasis includes topical agents, systemic agents and phototherapy. Several targets for psoriasis treatment have been used clinically and in clinical trials, such as at least 75% or 90% improvement in PASI, i.e. PASI75 or PASI90, or residual PASI scores of ≤ 4 or ≤ 2 [6].

Topical treatments used as first line (Table 3) include vitamin D analogues (e.g. calcipotriol, calcitriol) and topical corticosteroids. Of note, combination treatment with a topical corticosteroid and a vitamin D analogue (e.g. calcipotriol and betamethasone) was shown to be more effective than either agent alone and therefore represents a common choice in the treatment of mild chronic plaque psoriasis [26,27]. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) act by binding with the intercellular enzyme calcineurin and decreasing the activity of the nuclear factor of activated T cell (NFAT), leading to a reduced transcription of interleukin (IL)-2. These agents were shown to be effective in the treatment of psoriasis [28] and their use is particularly advantageous for treatment facial, genital and intertriginous areas. Other agents include topical retinoids, among which tazarotene is the agent most commonly used in plaque psoriasis and is particularly helpful for treating nail psoriasis. These agents influence genetic transcription of genes in keratinocytes by binding β and γ retinoic acid receptors on keratinocytes leading to reduced epidermal proliferation and normalized cell differentiation. Another topical drug is salicylic acid which possesses keratolytic

effect and can therefore be combined with other agents (including topical corticosteroids) in order to increase their penetration through scaly psoriatic plaques. While anthralin and coal tar preparations once represented the mainstay of psoriasis treatment, alone or in combination with phototherapy, these agents are now less frequently used as they stain and irritate the skin. More recently, two new topical medications have been approved for the treatment of psoriasis: tapinarof (an aryl hydrocarbon receptor agonist) and roflumilast (a phosphodiesterase 4 inhibitor). Although not yet available in Italy, these drugs appear promising options for the treatment of plaque psoriasis.

Phototherapy is used to treat moderate to severe plaque psoriasis and it works by inducing programmed cell death in T cells in both the epidermal and dermal psoriatic tissues [29]. Furthermore, apoptosis of keratinocytes in lesional and non-lesional epidermis and of Langerhans cell are observed. Broadband ultraviolet B light (bb-UVB, 290-320 nm) was first used to treat psoriasis. However, it was later replaced by narrowband ultraviolet B (nb-UVB, 311 nm), which was proved to be more effective [29]. Another option in relation to phototherapy is represented by PUVA (psoralen and ultraviolet A) therapy. While this is very effective for treating plaque psoriasis, its use is nowadays limited to selected cases as it carries an increased risk of squamous cell carcinoma of the skin, especially after 350 or more phototherapy sessions over a lifetime – a risk which is further increased by subsequent treatment with cyclosporin [30,31].

Conventional systemic drugs, including acitretin, methotrexate, cyclosporin and fumarates (Table 4), are used to treat moderate-to-severe psoriasis – defined as PASI >10 or BSA >10 and DLQI >10.

Acitretin is a retinoid indicated for treatment of moderate-to-severe psoriasis. While it can be used in monotherapy (especially in patients with comorbidities that contraindicate other agents such as in cancer patients), it is less effective than other conventional systemic and biologic agents and therefore it is commonly employed in lower doses as an adjunctive therapy to other treatments (e.g. phototherapy, biologics).

Table 3. Conventional systemic treatments used for chronic plaque psoriasis.

Drug	Mechanism of action	Adverse effects
Acitretin	Modulates the differentiation and proliferation of keratinocytes	Xerosis, cheilitis, xerophthalmia, hair loss, phototoxicity, hepatotoxicity, cutaneous infections, hyperlipidemia, intracranial hypertension, teratogenicity, depression
Methotrexate	Dihydrofolate reductase inhibitor	Nausea, mucosal ulceration, alopecia, fatigue, increased risk of infection, leukopenia, GI bleeding, hepatotoxicity, aplastic anemia, interstitial pneumonitis, teratogenicity
Cyclosporin	Calcineurin inhibitor (inhibits T cell activation)	Hypertension, renal toxicity, hypertrichosis, dyslipidemia, neurotoxicity, increased risk of infection, increased risk of cutaneous and lymphoproliferative malignancies

Methotrexate was shown to suppress T cell activation and adhesion molecule expression. Several mechanisms explain this effects, including dihydrofolate reductase inhibition, aminoimidazole carboxamide ribotide transformylase (AICARTase) blockade and adenosine accumulation. The drug is not only used to treat moderate-to-severe psoriasis, but it is also a first-line treatment in psoriatic arthritis. Its efficacy in psoriasis was shown by a randomized, double-blind,

placebo-controlled study which found that almost 40% of patients on methotrexate reached PASI75 at 16 weeks, compared with 18.9% of patients on placebo [32].

Cyclosporine is a calcineurin inhibitor used to treat moderate-to-severe psoriasis. Its efficacy was shown in several studies, including a 1-year, randomized study conducted on 400 patients in which significant improvement or complete remission was observed in 80-90% of patients within 12-16 weeks of treatment [33]. Its major advantage over other systemic agents is the rapid onset of action, which makes it an ideal choice in cases where rapid clearance is required (e.g. erythrodermic psoriasis).

Biologics are monoclonal antibodies or soluble receptors that target specific proinflammatory cytokines. The introduction of biologics has revolutionized the treatment of both psoriasis and psoriatic arthritis. While previously available conventional systemic agents are effective in plaque psoriasis, their use was limited by the numerous adverse effects which contraindicated their use in several subgroups of psoriatic patients with comorbidities. For example, methotrexate is contraindicated in patients with chronic hepatitis and cyclosporin in patients with refractory hypertension or history of malignancy. The advent of biologic drugs has made available new options in the armamentarium in psoriasis treatment which are not only more effective than conventional systemic agents, but also have a better safety profile. This is due to the fact that biologic drugs only block a specific cytokine (such as TNF- α , IL-17 or IL-23) unlike the generalized immunosuppression caused by the traditional immunosuppressants such as cyclosporin.

The classes of biologics currently approved for psoriasis are TNF- α inhibitors, IL-17 inhibitors, IL-12/23 inhibitor and IL-23 inhibitors [34]. Regarding TNF- α inhibitors (Table 5), etanercept is a recombinant human TNF- α receptor protein fused with the Fc portion of IgG1 binding soluble and membrane bound TNF- α . It is approved for moderate-to-severe chronic plaque psoriasis in both adults and children, psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis. In a phase 3 randomized placebo-controlled trial, 49% of patients treated with etanercept 50 mg reached PASI75 [35]. While less effective

than newer biologic agents, etanercept has an excellent safety profile and has been shown to also be safe in geriatric patients. Adalimumab is a recombinant, fully human, monoclonal antibody that blocks the interaction of TNF α with its cell-surface receptors. It is approved for adult and pediatric chronic plaque psoriasis, psoriatic arthritis, hidradenitis suppurativa, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and uveitis. It is regarded as a first line biologic treatment for psoriatic arthritis. In terms of efficacy, PASI 75/90/100 was achieved at week 16 in phase 3 trials by 71–79.6%, 37–48% and 11–14% of patients, respectively [36,37]. Certolizumab pegol is a humanized Fab antibody fragment conjugated to polyethylene glycol targeting TNF α . This unique structure allows the drug to have only minimal transfer across the placenta and into breast milk. Hence, the major advantage of certolizumab is its use in pregnant or breastfeeding patients. The drug is approved for chronic plaque psoriasis, psoriatic arthritis, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. In phase 3 trials (CIMPASI-1, CIMPASI-2 and CIMPACT), PASI75 was reached at 16 weeks by 66.5–81.4% (with the dose of 200 mg) and 74.7–82.6% (400 mg) of patients, and PASI90 by 35.8–52.6% (200 mg) and in 43.6–55.4% (400 mg) of patients [38,39]. Infliximab is a chimeric monoclonal antibody comprised of a murine variable region and a human IgG1-alpha constant region. It binds to soluble and transmembrane TNF α and is approved for the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis. In phase 3 EXPRESS1 and EXPRESS2 trials, PASI 75 and PASI90 were reached at week 10 by 75.5–80% and 45.2–57% of patients, respectively [40,41]. Unlike other TNF α inhibitors which are administered subcutaneously, infliximab is administered intravenously and allows rapid control of psoriasis. It is therefore useful for patients with erythrodermic psoriasis or acute generalized pustular psoriasis in which rapid onset of action is required. Safety concerns associated with TNF α inhibitors are injection site reactions, upper respiratory tract infections, neutropenia, infections, malignancies, worsening of congestive heart failure, drug-induced lupus and demyelinating disorders. Regarding infections, screening for viral hepatitis, HIV and tuberculosis is needed

before treatment initiation as these agents may reactivate e.g. latent tuberculosis or chronic occult viral hepatitis. Furthermore, treatment with these agents is not recommended in patients with a recent (< 5 years) history of malignancy.

Table 4. TNF- α inhibitors approved for chronic plaque psoriasis.

Drug	Brand name	Structure	Dosing
Etanercept	Enbrel®	TNFR and IgG Fc fusion protein	50mg/week
Adalimumab	Humira®	Human IgG1 κ	80mg (loading dose), then 40mg every 2 weeks
Certolizumab pegol	Cimzia®	PEGylated Fab fragment of humanized IgG1	400mg at weeks 0, 2 and 4, then 200mg every 2 weeks
Infliximab	Remicade®	Human-murine chimeric IgG1	5mg/kg at weeks 0, 2 and 6, then every 8 weeks

Regarding IL-17 inhibitors (Table 6), secukinumab is a fully human IgG1 κ monoclonal antibody targeting IL-17A currently approved for adult and pediatric chronic plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and active non-radiographic axial spondyloarthritis. In phase 3 trials (ERASURE, FIXTURE), PASI 75/90/100 at 12 weeks was achieved by 77.1–81.6%, 54.2–59.2% and 24.1–28.6% of patients, respectively [42]. Secukinumab has also shown superior efficacy in head-to-head trials against both etanercept and ustekinumab [43]. Ixekizumab is a humanized IgG4 monoclonal antibody targeting IL-17 approved for adult and pediatric chronic plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. In an integrated efficacy analysis of phase 3 trials (UNCOVER-1, UNCOVER-2, UNCOVER-3), PASI 75/90/100 was reached at 12 weeks by 88.7%, 69.9% and 37.6% of patients on ixekizumab compared to 47.7%, 22.3% and 6.4% of patients on etanercept [44]. Brodalumab is a human IgG2 monoclonal antibody that binds with high affinity to human IL-17RA and blocks IL-17A, IL-17F and IL-17A/F heterodimer. It is

currently only approved for the treatment of chronic plaque psoriasis. In phase 3 trials (AMAGINE-1, AMAGINE-2 and AMAGINE-3), PASI75/90/100 was achieved at week 12 by 83.3–86%, 70.3% and 37–44% of patients [45,46]. Bimekizumab, the newest drug in the class, is a IgG monoclonal antibody targeting a peptide region shared by IL-17A and IL-17F. Clinical trials have shown efficacy in psoriasis (with superior response compared with ustekinumab [47]) and, more recently, in psoriatic arthritis. In a phase 3 trial, 85% of patients on bimekizumab reached PASI90 at 16 weeks compared with 50% of patients on ustekinumab [47]. Other than in psoriasis and psoriatic arthritis, the drug is also currently approved for active non-radiographic axial spondyloarthritis.

Advantages of IL-17 inhibitors over other biologics include the excellent safety profile and fast onset of action. Furthermore, they are effective in psoriatic arthritis: for example, head-to-head studies of ixekizumab against adalimumab found to similar control of symptoms and inhibition of joint destruction and bone erosion [48]. Safety concerns of IL-17 inhibitors include injection site reactions, upper respiratory tract infections, neutropenia, fungal infections (including mucocutaneous candidiasis) and the development of inflammatory bowel disease (IBD). Alongside the contraindications shared with other classes of biologics, this class is particularly contraindicated in patients with personal history of IBD. Ultimately, the Food and Drug Administration (FDA) issued a black box warning after six patients on brodalumab across four clinical trials committed suicide. Although no causal relationship was identified, brodalumab is currently contraindicated in patients with depression.

Table 5. IL-17 inhibitors approved for chronic plaque psoriasis.

Drug	Brand name	Structure	Target	Dosing
Secukinumab	Cosentyx®	Human IgG1k	IL-17A	300mg at weeks 0,1,2,3,4, then every 4 weeks
Ixekizumab	Taltz®	Humanized IgG4	IL-17A	160mg at week 0, then 80mg at weeks 2,4, 6,8,10,12, then 80mg every 4 weeks
Brodalumab	Kyntheum®	Human IgG2	IL-17RA	210mg at weeks 0,1,2, then every 2 weeks
Bimekizumab	Bimzelx®	Humanized IgG1	IL-17A, IL-17F, IL-17AF	320mg at week 0,4,8,12,16 then every 8 weeks

Regarding IL-12/23 inhibitor (Table 7), ustekinumab is a human monoclonal antibody targeting the p40 subunit of both IL-12 and IL-23. A peculiarity of this agent is its weight-based dosing, with a dose of 45 or 90 mg used in patients weighing less or more than 100 kg respectively. It is approved for the treatment of adult and pediatric chronic plaque psoriasis, Crohn's disease and ulcerative colitis. In phase 3 trials PHOENIX 1 and PHOENIX 2, PASI75 at week 12 was reached by 66.7–67.1% of patients on ustekinumab 45 mg and 66.4–75.7% of patients on ustekinumab 90 mg of patients, while PASI90 by 41.6%–42.3% (45 mg) and 36.7–50.9% (90 mg) [49,50]. Although less effective than newer biologics such as IL-17 inhibitors and IL-23 inhibitors, ustekinumab has an excellent safety profile as in more than 20 years of safety data no evidenced based increase in serious adverse effects was found. The most common adverse effects reported are upper respiratory tract infections and injection site reactions. Furthermore, it is one of the biologics - alongside with risankizumab and tildrakizumab - that requires the lowest number of injections per year (4/year, every 12 weeks).

Regarding IL-23 inhibitors (Table 7), guselkumab is a fully human IgG1 λ monoclonal antibody targeting the p19 subunit of IL-23 currently approved to treat moderate-to-severe plaque psoriasis and psoriatic arthritis. The drug was shown to be highly effective in psoriasis with 73% of patients reaching PASI90 at 16 weeks in the VOYAGE 1 trial [51]. Furthermore, the drug was found to be more effective than secukinumab in reaching PASI90 at week 48 [52]. Another inhibitor of the p19 subunit of IL-23 is risankizumab, a humanized IgG1 monoclonal antibody approved for the treatment of psoriasis and psoriatic arthritis. Risankizumab was found to have high efficacy in psoriasis: in phase 3 ULTIMMA-1 and ULTIMMA-2 trials, PASI90 was achieved by 75.3% and 74.8% of patients at week 16 respectively [53]. Furthermore, other clinical trials have proved superior efficacy compared with adalimumab, ustekinumab, and secukinumab [54,55]. Other advantages of this agent are the high durability and its dosing schedule, with a maintenance administered subcutaneously every 12 weeks. Also, tildrakizumab is a humanized IgG1 monoclonal antibody targeting the p19 subunit of IL-23 approved for plaque psoriasis. Several phase 3 trials showed superior efficacy to both placebo and etanercept: in reSURFACE 1, 80.4% and 51.6% of patients treated with tildrakizumab 100 mg achieved PASI75 and PASI90 at week 28 respectively [56]. In reSURFACE 2, 73.5% and 55.5% of patients treated with tildrakizumab 100 mg reached PASI75 and PASI90 at week 28 compared with 53.6% and 29.4% of those treated with etanercept [56]. In regard to the safety profile of IL-23 inhibitors, no significant safety concerns were observed with these agents, with no increased risk of tuberculosis or of serious infections. The most common adverse reactions include upper respiratory infection and injection site reactions. The safety of these agents represents therefore a significant advantage in the treatment of psoriatic patients who have contraindications to other agents, such as patients with IBD.

Table 6. IL-12/23 and IL-23 inhibitors approved for chronic plaque psoriasis.

Drug	Brand name	Structure	Target	Dosing
Ustekinumab	Stelara®	Human IgG1k	p40 subunit of IL-12 and IL-23	45mg (if pt weight <100 kg) at weeks 0,4, then every 12 weeks
Guselkumab	Tremfya®	Human IgG1λ	p19 subunit of IL-23	100mg at weeks 0,4, then every 8 weeks
Risankizumab	Skyrizi®	Humanized IgG1	p19 subunit of IL-23	150mg at weeks 0,4, then every 12 weeks
Tildrakizumab	Ilumetri®	Humanized IgG1k	p19 subunit of IL-23	100mg weeks 0 and 4, then every 12 weeks

In conclusion, biologic agents have had a dramatic impact on outcomes in moderate–severe psoriasis thanks to their superior efficacy and safety profile compared to conventional systemic agents. Furthermore, the recent introduction of several biologics targeting different cytokines has allowed psoriasis treatment to become tailored to the needs of each patient. For example, psoriasis severity, coexistence of psoriatic arthritis, previous treatment failures, comorbidities (e.g. demyelinating disease, cancer, IBD), desire to conceive, need to breastfeed, dosing frequency are all factors which influence the choice of an agent over another. Despite their favorable efficacy and safety profile, however, the use of biologic treatment is limited by their high cost as described in a subsequent section. Furthermore, these agents (like conventional systemic agents) require regular clinical and laboratory monitoring to ensure early detection of possible (albeit rare) adverse events. Ultimately, subcutaneous or intravenous administration is required, which may represent a problem for patients with injection/needle phobia.

The last group of drugs used to treat chronic plaque psoriasis are oral small-molecules inhibitors - agents characterized by a low molecular weight (<1000 Dalton) that modulate cytokines by influencing intracellular signaling pathways. Compared to biologics, oral small-molecules inhibitors are administered orally (which may represent a significant advantage for a subgroup of psoriasis patients

including those with needle phobia) and are easier to synthesize – which translates in lower manufacturing costs. Currently approved small molecules for psoriasis are apremilast, dimethylfumarate and deucravacitinib (Table 8).

Apremilast inhibits phosphodiesterase 4 (PDE4), leading to increased levels of cAMP intracellularly which in turn results in the inhibition of the production of proinflammatory cytokines and promotion of the production of anti-inflammatory mediators. Apremilast is approved to treat chronic plaque psoriasis and psoriatic arthritis. In phase 3 clinical trial ESTEEM 1, significantly more patients taking apremilast achieved PASI75 at 16 weeks than those on placebo (33.1% vs 5.3%) [57]. While the drug is less effective than biologic agents, is nevertheless safe with a very low risk of serious side effects and therefore requires no laboratory monitoring. It can also be administered safely in patients with history of cancer. A few common ($\geq 5\%$ of patients) mild to moderate side effects have been reported, including diarrhea, nausea, headache, and nasopharyngitis. Gastrointestinal adverse effects (especially diarrhea) in particular are the most common ones and may sometimes require drug discontinuation.

Dimethylfumarate inhibits NF- κ B translocation thus leading to a downregulation of inflammatory cytokines. In a recent phase 4 clinical trial, 46.0%/24.8%/10.9% of patients achieved PASI75/90/100 response at week 24, respectively [68]. In that study, the most common adverse events were gastrointestinal complaints (diarrhea/abdominal pain in 50.0%/35.1% of patients respectively), flushing (28.0%) and lymphopenia (31.2%) [58].

The most recently approved oral small molecule inhibitor, deucravacitinib, belongs to the class of Janus kinase (JAK) inhibitors. Several cytokines involved in the pathogenesis of psoriasis (such as IL-12, IL-23, IL-17, IL-19, and TNF α) bind to receptors which use the JAK–signal transducer and activator of transcription (STAT) pathway for signaling.

As one of these cytokines binds to the receptor, the receptor undergoes a conformational change and recruits two JAK proteins, which in turn become activated and alter the receptor to enable the recruitment of two STAT molecules.

Table 7. Oral small molecules approved for chronic plaque psoriasis.

Drug	Brand name	Mechanism of action	Dosing
Apremilast	Otezla®	Phosphodiesterase 4 (PDE4) inhibitor	30 mg twice a day
Dimethylfumarate	Skilarence®	Inhibits NF-kB translocation	Up to 120 mg three times a day
Deucravacitinib	Sotyktu®	Tyrosine kinase 2 (TYK2) inhibitor	6 mg once a day

The receptor-bound STAT molecules phosphorylate, dimerize and then translocate to the nucleus. In the nucleus, the STAT dimer serves as transcription factor influencing gene expression.

First-generation JAK inhibitors block multiple JAK proteins and are thus able to interfere with several downstream signaling pathways. While such agents gained approval in other dermatological diseases, they did not in psoriasis because of the unfavorable safety profile in psoriatic patients. Subsequent research focused on the development of more targeted and safer agents. In this regard, deucravacitinib (BMS-986165) is an oral tyrosine kinase 2 (TYK2) selective inhibitor approved for the treatment of moderate to severe chronic plaque psoriasis and psoriatic arthritis. TYK2 plays a crucial role in the pathogenesis of psoriasis as it is involved in the signaling of IL-12, IL-23 and type 1 interferon and hence in the development of Th1 and Th17 cells. Unlike other JAK inhibitors which act as ATP competitors and possess limited specificity and therapeutic index, deucravacitinib binds to the regulatory domain of TYK2, and this allows a more selective activity. In terms of safety, data on deucravacitinib from clinical trials appear reassuring as there was no increased incidence of adverse events, serious adverse events or adverse event-related treatment discontinuation [59]. The most common adverse events included nasopharyngitis, headache, diarrhea, nausea, upper respiratory tract infections and acne. In terms of efficacy, deucravacitinib was shown to be more effective than placebo and apremilast: in the POETKY

PSO-1 trial, PASI75 was reached by 58.4% of patients on deucravacitinib at week 16 as opposed to 12.7% and 35.1% of patients on placebo and apremilast, respectively [60].

Biosimilars in psoriasis

A biosimilar is a biologic medicine which is highly similar to an already approved biologic drug (known as reference biologic or originator) [61]. Unlike generic drugs which are synthesized from chemicals, biosimilars are produced using cell lines and their complex production implies that they cannot be exactly identical to the reference biologic. However, they must not show clinically meaningful differences in terms of safety, purity and efficacy compared to the originator [62]. In order for a biosimilar to be approved, it must undergo extensive testing including analytical studies, structural/functional comparisons, pharmacokinetics and pharmacodynamics testing and “equivalence” clinical trials to assess their safety, efficacy and immunogenicity compared with the originator [62]. Such equivalence trials generally are conducted on the most common indication of a biologic (e.g. rheumatoid arthritis for adalimumab) and are then extrapolated to other therapeutic indications using comparability studies. The list of reference biological drugs and their biosimilars currently available for plaque psoriasis are listed in Table 8.

Efficacy: clinical trials

Only a small number of biosimilar equivalence trials were conducted on plaque psoriasis, as most trials were conducted on rheumatological indications. Randomized clinical trials conducted on psoriasis have all shown that the efficacy of the biosimilar drugs tested was comparable with that of the originator.

Infliximab

Regarding infliximab, the 52-week randomized NOR-SWITCH trial found that switching from reference infliximab to CT-P13 was not inferior to treatment with the originator in patients with plaque psoriasis, psoriatic arthritis, spondyloarthritis, rheumatoid arthritis, Crohn’s disease and ulcerative colitis [63].

Table 8. Currently available biosimilars approved in the European Union for chronic plaque psoriasis (modified from [61]).

Originator drug	Originator brand name	Biosimilar drug	Biosimilar brand name
Infliximab	Remicade®	CT-P13	Inflectra®/Remsima®
		SB2	Flixabi®
		PF-06438179/GP1111	Ixifi®/Zessly®
Etanercept	Enbrel®	SB4	Benepali®
		GP2015	Erelzi®
Adalimumab	Humira®	ABP 501	Amgevita®
		SB5	Imraldi®
		BI 695501	Cyltezo®
		FKB327	Hulio®
		GP2017	Hyrimoz®/Halimatoz®
		MSB11022	Idacio®
		PF-06410293	Amsparity®
		CT-P17	Yuflyma®
Ustekinumab	Stelara®	AVT02	Hukyndra®/Libmyris®
		AVT04	Uzpruvo®
		SB17	Pyzchiva®/Eksunbi®
		ABP 654	Wezenla®
		FYB202	Fymkina®
		DMB-3115	Imuldosa®
		CT-P43	SteQeyma®
		KFCE	Yesintek®

Etanercept

The EGALITY double-blind randomized trial compared originator etanercept and GP2015 in patients with plaque psoriasis using a multiple-switch design. Patients who reached PASI50 at week 12 were re-randomized to continue the same treatment or to undergo a sequence of three switches between GP2015 and originator etanercept until week 30. The study found equivalent efficacy of originator etanercept and GP2015, with a difference in PASI 75 at week 12 between GP2015 and ETN of -2.3% [64].

Adalimumab

A 52-week double-blind randomized phase III clinical trial compared the efficacy and safety of ABP 501 with originator adalimumab [65]. At week 16, patients on ABP 501 who reached PASI50 continued the same treatment, while patients on originator adalimumab were re-randomized to receive originator adalimumab or ABP 501. At week 16, no differences in efficacy between the two drugs were found: PASI improvement was 80.9% for ABP 501 and 83.1% for originator adalimumab [65]. Furthermore, a phase III randomized clinical trial that assessed the interchangeability of CT-P17 with reference adalimumab in psoriasis patients found comparable efficacy between the continuous and switching arms [66]. Lastly, a phase III randomized clinical trial which compared AVT02 with reference adalimumab in patients with plaque psoriasis found equivalent efficacy between the two treatment groups, with PASI improvement at week 16 of 91.6% for AVT02 and 89.6% for originator adalimumab [67].

Ustekinumab

A 52-week randomized study which compared AVT04 with originator ustekinumab in patients with psoriasis found equivalent efficacy between the two treatments, with a PASI improvement at 12 weeks of 87.3% for AVT04 vs 86.8% for originator ustekinumab [68]. Similarly, another randomized phase III clinical trial comparing SB17 with originator ustekinumab found equivalent efficacy of the two treatments, with an adjusted difference of PASI change from baseline at week 12 of -0.6% (95% CI -3.780, 2.579) which was within the $\pm 15\%$ equivalence margin [69]. Regarding ustekinumab biosimilar CT-P43, a phase III randomized clinical trial found that it demonstrated equivalent efficacy to originator ustekinumab in patients with plaque psoriasis, with a mean improvement in PASI at week 12 of 77.93% for CT-P43 and 75.89% for originator ustekinumab [70]. Lastly, a 52-week randomized single-transition comparative clinical study compared ABP 654 with originator ustekinumab in patients with plaque psoriasis and found similar efficacy between the two treatments. The mean difference in percentage PASI improvement at 12 weeks between the two treatment groups was 0.14 (90% CI -2.6-2.9), which was within the prespecified ± 10 similarity margin [71].

Efficacy: real world data

Infliximab

Regarding infliximab biosimilar CT-P13, its efficacy was confirmed in a 1-year real-world prospective post-marketing surveillance Japanese study which found that, among bio-naïve patients treated with CT-P13, 55% reached an absolute PASI score <1 at 30 weeks [72]. Furthermore, the study included 105 patients switched from reference infliximab to CT-P13: of those, 57% had already reached PASI <1 and maintained this status after switching [72]. Furthermore, an Italian real-world study on psoriasis patients treated with CT-P13 found no changes in PASI in the 30 patients switched from infliximab originator to CT-P13 [73]. Similarly, sustained efficacy after switching from reference infliximab to CT-P13 was reported in a real-world study based on the Italian Psobiosimilars registry [74]. Another study assessed psoriatic patients switched from one infliximab biosimilar (CT-P13) to another infliximab biosimilar (SB2) and found no changes in PASI in the 6-month observation period after switching [75]. Also, a 94-week Polish registry study on 91 psoriatic patients treated with infliximab biosimilars confirmed high and sustained clinical efficacy (PASI 75/90/100 were achieved at 14 weeks by 83.52%, 49.45% and 26.37%) [76].

Etanercept

A real-life study involving 65 patients with psoriasis that compared SB4 with originator etanercept for up to 24 months of treatment demonstrated equivalence between the two drugs in terms of absolute PASI and non-inferiority in terms of PASI 75 and PASI90 rates [77]. Furthermore, no changes in efficacy in patients with psoriasis switched to SB4 were reported in a study based on the Italian Psobiosimilars registry [78]. Lastly, a real-world study based on the Danish DERMBIO registry which included patients who switched from originator etanercept to SB4 and from originator infliximab to CT-P13 found no significant differences in discontinuation risk between originator and biosimilar versions of infliximab or etanercept [79].

Adalimumab

In a large multinational real-world cohort study, which included 7387 biosimilar new users and 3654 switchers matched with reference adalimumab users found no

differences in all-cause discontinuation between biosimilar and reference adalimumab new users [80]. Additionally, a British real-world study based on data from the BADBIR registry which 11400 included psoriatic patients found that patients starting adalimumab biosimilars ABP 501 and SB5 had no different probability of reaching PASI ≤ 2 or ≤ 4 compared to those on reference adalimumab [81]. Also, patients who switched from originator adalimumab to those two biosimilars had no different probability of reaching PASI ≤ 2 or ≤ 4 compared to those who continued reference adalimumab [81]. Lastly, a real-world study based on the Patients in the Biological Treatment in Danish Dermatology (DERMBIO) registry assessed the outcomes of mandatory nonmedical switch from reference adalimumab to adalimumab biosimilars (GP2017 or SB5) in patients with psoriasis. The 1-year drug retention in patients switching to adalimumab biosimilars was comparable to that of patients treated with adalimumab originator (92.0% vs 92.1%) [82].

Drug survival

Regarding infliximab, a 1-year real-world prospective post-marketing surveillance Japanese study found that among patients switched from reference infliximab to biosimilar CT-P13 the drug survival rate at 1 year was as high as 74% [72].

Regarding etanercept, a real-world study based on the British register BADBIRD found that psoriatic patients on SB4 had a discontinuation rate of at 12 months of 24.4%, which was comparable with the discontinuation rate of reference etanercept reported in the BADBIR registry [83].

Regarding adalimumab, a real-world study based on the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) found that the average real life drug survival of SB5 in patients with psoriasis was 2.5 years, which was similar to the originator [84].

Safety

Infliximab

Regarding infliximab, a 1-year real-world prospective post-marketing surveillance Japanese study on psoriatic patients treated with CT-P13 found no safety concerns. In particular, adverse drug reactions (ADRs) occurred in 29 patients

(17.6%) and were mostly infusion reactions (6.7%), while serious ADRs were reported in only in 1.2% [72]. Furthermore, no safety concerns were found in a real-world integrated analysis of three Japanese observational studies which included 1816 patients treated with CT-P13 (including 165 patients with psoriasis): in that study, adverse drug reactions were reported in 24.2% of all patients [85]. Similarly, no safety concerns after switching from reference infliximab to CT-P13 were reported in a real-world study based on the Italian Psobiosimilars registry [74].

Etanercept

In the EGALITY study, a randomized, double-blind study comparing GP2015 with originator etanercept, the incidence of treatment-emergent adverse events up to 52 weeks was equivalent between GP2015 and originator etanercept (59.8% and 57.3% respectively) [64]. Furthermore, no changes in adverse effect incidence were found in patients with psoriasis switched to SB4 in a study based on the Italian Psobiosimilars registry [78]. Another real-world study based on the BADBIR registry found a low incidence of adverse events in psoriasis patients treated with GP2015 [86].

Adalimumab

In a 52-week phase III trial comparing ABP 501 with originator adalimumab, no new safety signals were detected while adverse events were balanced between the two treatment groups [87]. Furthermore, the VOLTAIRE-X phase III clinical trial assessed the safety of multiple switches between reference adalimumab and BI 695501 in patients with plaque psoriasis and found comparable safety between the switching and continuous treatment arms [88]. Another phase III randomized clinical trial that assessed the interchangeability of CT-P17 with reference adalimumab in psoriasis patients found comparable safety between the continuous and switching arms [66]. Moreover, in a phase III randomized clinical trial which compared AVT02 with reference adalimumab in patients with plaque psoriasis, the safety profile was comparable between the two treatment groups [67].

Real-evidence data confirmed the safety of adalimumab biosimilars. In particular, a large multinational real-world cohort study found a similar risk of adverse events between biosimilar new users and reference adalimumab new users

(incidence rate ratio 0.91, 95% CI 0.80-1.05) and between switchers and continuous reference adalimumab users (incidence rate ratio 0.92, 95% CI 0.83-1.01) [80].

Ustekinumab

A 52-week randomized study which compared AVT04 with originator ustekinumab in patients with psoriasis found equivalent safety profiles for the two treatments [68]. Similarly, another randomized phase III clinical trial comparing SB17 with originator ustekinumab found comparable overall treatment-emergent adverse events between the two treatments (48.2% for SB17 and 48.8% with originator ustekinumab) [69]. Also, a phase III randomized clinical trial which compared CT-P43 with reference ustekinumab found equivalent safety outcomes between treatment groups, including after switching from reference ustekinumab to CT-P43. [70]. Lastly, a 52-week randomized single-transition comparative clinical study compared ABP 654 with originator ustekinumab in patients with plaque psoriasis and found similar safety profiles between the two treatment groups [71].

Biosimilar utilization for psoriasis in Europe

Regarding TNF- α inhibitor biosimilars, their market share in the European Union in 2023 was 69%, but there were considerable differences across European countries. Considering the largest European markets, the highest biosimilar market shares were observed in Denmark (91%) and in the United Kingdom (86%); Italy (77%), Spain (75%) and Germany (71%) were slightly above the European average while France (58%) was slightly below [89]. There is currently no data on the market share of ustekinumab biosimilars due to their recent introduction.

Biosimilar regulatory framework and pricing policies in Europe

A biosimilar is defined by the European Medicines Agency as “biological medicine highly similar to another biological medicine already approved in the European Union (called “reference medicine”) in terms of structure, biological activity and efficacy, safety and immunogenicity profile” [90]. Biosimilars are

authorized by EMA through a centralized procedure, and such an authorization is effective in every European Union state. However, pricing and regulatory policies vary significantly across Europe. Regarding pricing, several mechanisms are employed in different European countries such as free pricing, mandatory discounts, framework agreements, single- or multi-winner tenders organized at a regional and/or national level. Another important aspect regarding biosimilar regulation concerns interchangeability. The European Medicines Agency and the Heads of Medicines Agencies issued a joint statement on biosimilar interchangeability, meaning that EU-approved biosimilars can be used in place of the reference product or other biosimilars of the same reference product [91]. However, interchangeability policies are de facto decided by individual member countries, which set different penetration targets and adopt various policies to promote interchangeability - including pharmacy substitution, mandatory switching, prescription quotas and incentives to hospitals or physicians. In the following paragraphs, the regulatory and pricing policies of the largest European countries will be discussed as these countries act as trend-setters for the rest of Europe.

France

In France, biosimilar pricing policies differ between the hospital market segment and the retail segment. In the hospital market segment, France's Economic Committee on Health Care Products (CEPS) demands a 30% price cut on biosimilar and originator. Later, after 24 and 48 months, 10% to 30% additional price cuts are applied. Biosimilars are purchased mainly through multi-winner tenders or to a lower extent through negotiated agreements [92]. Of note, France provides financial incentives to hospitals for prescribing biosimilars, namely 20% of the price difference between the original biologic and its biosimilars.

In the retail market segment, the CEPS sets the price of biosimilars 40% below the price of the originator while the original biologic is imposed a price cut of 20%. Later, at 24 and 42 months after the entry of the first biosimilar, additional price cuts (5% to 15%) are imposed according to the market share [92]. Office-based physicians are given incentives if they prescribe a group of seven biosimilars (including etanercept and adalimumab) through initiations or switches.

The 2018–2022 National Health Strategy document set a goal of 80% biosimilars penetration [92].

Germany

In Germany, the federal and regional governments delegate certain healthcare responsibilities to Statutory Health Insurance (SHI; German: Gesetzliche Krankenversicherung (GKV)) or Private Health Insurance (PHI; German: Private Krankenversicherung (PKV)) scheme. Within SHI, the main payers are membership-based not-for-profit insurance companies (sickness funds; German: Krankenkassen) which may be at a national or at the regional level. Furthermore, in Germany, there is a clear distinction in the provision of outpatient and hospital care. Price setting for pharmaceuticals in the hospital market is unregulated and established through direct hospital-manufacturer negotiations. In the outpatient sector, insurance companies rely on the organization of framework agreements named “open-house rebate contracts” (German: Open-House-Rabattverträge) awarded via multi-winner tenders [93]. Biosimilars are allowed free pricing, but there are restrictions, as Germany utilizes international reference pricing (IRP) as a price control mechanism. Furthermore, all suppliers of originator biologics and biosimilars can participate in “open-house rebate contracts” if they adhere to certain pre-defined contractual conditions, including mandatory discounts on list prices [93]. These conditions are freely set by the insurer and are strictly confidential (prices paid by insurers for biosimilar drugs are not even available to prescribers).

Every year, the National Association of Statutory Health Insurance Funds (German: Gesetzliche Krankenversicherung-Spitzenverband (GKV-SV) and National Association of Statutory Health Insurance Physicians (KBV, i.e. Kassenärztliche Bundesvereinigung) set recommendations for biosimilar use and prescribing targets at a national level. Insurance companies and regional physician associations, based on the national advisory agreement, define implementation details which are binding at the regional level [93]. More recently, from 2024, pharmacies in Germany can automatically substitute a prescribed biologic with a biosimilar with a more favorable price.

Italy

In Italy, while the planning of health services is organized by regional health authorities, the central Italian National Health Service (SSN) controls the healthcare budget and sets the ceiling for regional hospital pharmacy spending. The Italian Medicines Agency (AIFA) oversees pricing of medicines and demands that the price of biosimilars is at least 20% lower than the originator's price. Then, biosimilars are purchased by regional health authorities using framework agreements awarded via tenders [94]. According to the 2017 Budget Law, when more than three medicines with the same active principle are marketed (including biologic originator and biosimilars), public purchasing procedures via framework agreements need to be carried out. The regional contracting authorities are bound to close purchasing agreements with all three winners of the tender. However, given unclear criteria for the division of supply quotas among the three winners, some Italian regions have been purchasing biosimilars only through the first-ranked winner manufacturer [94]. Another aspect that has not been clarified is whether prescribers should prefer the first-ranked drug or prescribe any of the three winners indifferently.

Regarding interchangeability, AIFA considers that the originator biologic and its biosimilars as interchangeable, yet the decision on treatment initiation and switching belongs to the physician. Some regional administrations have implemented biosimilar quotas and switching protocols to increase biosimilars penetration. For example, Piemonte and Toscana require physicians to provide justification if they choose to use the originator in a patient that is eligible for switching to a more cost-effective biosimilar [94]. In conclusion, the different policies on interchangeability and biosimilar promotion have led to a heterogeneous scenario in terms of utilization and penetration of biosimilar drugs across different Italian regions.

Spain

In Spain, the management of health services and budgets has been transferred from the central government to the 17 largely autonomous regional administrations. However, medicines pricing and reimbursement decisions are made centrally. The Spanish Agency of Medicines and Medical Devices

(AEMPS) controls the approval of medicines, while the Interministerial Pricing Commission (CIPM) controls their pricing. CIPM demands that prices for biosimilar medicines must be 30% lower than originators' prices [94]. Biosimilars are only dispensed by hospital in Spain. Of note, net prices paid by hospitals for biosimilars are much lower than the prices set by the CIPM, due to direct hospital-manufacturer negotiations and framework agreements awarded via tenders (single-winner or multi-winner) organized at both a national and regional level [95]. Regarding the central procurement of biosimilars, the National Institute of Healthcare Management (INGESA) has been preparing a framework agreement proposal for the procurement of off-patent biologics and biosimilars since 2021. These agreements have a duration of 2 years, and the regions are allowed to decide whether they want to adhere to this agreement (most regions did agree) [94]. Although biologics cannot be substituted by community pharmacists, Pharmacy and Therapeutics Committees within hospitals can decide on the interchangeability of biologics and agree on switching protocols [94].

United Kingdom

The Medicines and Healthcare products Regulatory Agency (MHRA) approves biosimilar drugs and organizes multiple-win tenders at multiple levels. The United Kingdom allows manufacturers to set prices, even for biosimilars. Of note, multi-winner tenders create a sustainable market by maintaining competition while sharing total volume between several manufacturers.

Targets for biosimilar penetration set by the National Healthcare System (NHS) include: 100% of new patients requiring biological medicines initiated on the best value biological within 3 months following its launch and at least 80% of existing patients on the best value biological medicine within 10 months of its launch [96]. Despite the absence of mandatory discounts, biosimilars had the highest price erosion in the United Kingdom compared to other European markets, likely due to centralized negotiations and switching policies mandated by the NHS [97].

Denmark

Biologics are provided through hospitals, and the Danish central procurement agency (Amgros) organizes single-winner tenders at a national level [98]. The two main disadvantages of such single-winner tenders are lower security of supply (in

case of disruption of the supply chain of the manufacturer) and less competition. Indeed, because a single manufacturer dominates the market, competitors might be dissuaded from participating in further tenders. In contrast, multi-winner tenders reward multiple biosimilar developers with smaller contracts and thus maintain marketplace competition [99]. Furthermore, from 2015, Denmark introduced mandatory switching from originator to biosimilar and biosimilar-to-biosimilar. These policies allow Denmark to have the fastest and most thorough biosimilar uptake in Europe (with a 90% market share three months after first sales) [100].

Comorbidities

Multimorbidity, which is defined as the presence of two or more chronic conditions, is common in individuals with psoriasis. The most commonly associated comorbidities in patients with plaque psoriasis are listed in Table 9.

Psoriatic arthritis is the most important comorbidity of plaque psoriasis and consists of a heterogenous inflammatory arthritis with joint and/or enthesal inflammation that can coexist with extra-articular manifestations [101]. The prevalence of psoriatic arthritis is estimated to fall in the 20–30% range, depending on many factors, including patient ethnicity and the diagnostic criteria used [101]. Most commonly (in approximately 70–80% of patients) psoriasis precedes the development of psoriatic arthritis, although in 10–15% of patients there is simultaneous onset of psoriasis and psoriatic arthritis and in 10–15% the articular involvement precedes the cutaneous one [101].

Several factors have been found to influence the risk of developing psoriatic arthritis in psoriatic patients: for instance, greater psoriasis severity and higher disease duration represent risk factors for the development of psoriatic arthritis [101]. Of note, however, cutaneous severity is only weakly associated with joint disease severity. Furthermore, certain psoriasis localizations (such as nail, scalp, intergluteal, perianal) represent risk factors for the development of psoriatic arthritis.

Table 9. List of the most common diseases associated with plaque psoriasis

Comorbidities associated with psoriasis
Psoriatic arthritis
Cardiovascular diseases
Hypertension
Myocardial infarction
Coronary artery disease
Stroke
Metabolic diseases
Dyslipidemia
Diabetes mellitus (type 2)
Obesity
Metabolic syndrome
Nonalcoholic fatty liver disease (NAFLD)
Inflammatory bowel diseases (IBD)
Malignancy (including lymphoma)
Mental diseases
Depression
Anxiety
Suicidal ideation

Clinically, psoriatic arthritis can have heterogenous presentations which may coexist, including peripheral arthritis, axial arthritis, enthesitis and dactylitis. The diagnosis of psoriatic arthritis relies mainly on the “CASPAR” (Classification for Psoriatic Arthritis) criteria, which are shown in Table 10 [102]. In order for the diagnosis of psoriatic arthritis to be made, the patient must have inflammatory joint disease and score at least 3 points on other parameters.

Although the diagnosis of psoriatic arthritis is a clinical one, screening questionnaires, elevated acute phase reactants and imaging studies such as ultrasound, X-ray and magnetic resonance imaging (MRI) are often helpful to reach the diagnosis.

Table 10. CASPAR (Classification for Psoriatic Arthritis) criteria.

Entry criterion:	
Articular disease (joint, spine, enthesal)	
Criterion	Points
Current psoriasis	2
Personal history of psoriasis	1
Family history of psoriasis	1
Psoriatic nail dystrophy (onycholysis, pitting, and hyperkeratosis)	1
Negative rheumatoid factor	1
Current dactylitis or history of dactylitis (recorded by a rheumatologist)	1
Juxta-articular new bone formation on hand or foot X-ray	1

Psoriasis is also associated with an increased risk of cardiovascular diseases including acute myocardial infarction, coronary artery disease and stroke. While psoriatic patients also have an increased incidence of traditional cardiovascular risk factors such as dyslipidemia, metabolic syndrome and obesity which contribute to elevate their cardiovascular risk, it is worth noting that psoriasis *per se* is an independent risk factor for cardiovascular disease. Two meta-analyses found that the risk of major cardiovascular events (i.e. myocardial infarction, stroke, and cardiovascular mortality) was increased among patients with psoriasis especially in those with severe psoriasis or longer disease duration [103]. Importantly, the risk of myocardial infarction was shown to be significantly increased – although to a lesser extent - in both meta-analyses even in patients with mild psoriasis. This suggests that the increased cardiovascular risk incurred by patients with psoriasis is not limited to severe psoriasis. The rationale behind the association between psoriasis and cardiovascular diseases has yet to be fully elucidated. It has been proposed that the chronic low-grade inflammation observed in psoriasis causes premature atherosclerosis via shared immunopathogenic mechanisms. There is still controversy, however, as to

whether the association is only explained by chronic inflammation and to what extent, on the other hand, by the increased prevalence of cardiovascular risk factors [104].

Furthermore, psoriasis was shown to be associated with hypertension in a meta-analysis which found a pooled odds ratio (OR) of 1.58 (95% CI 1.42–1.76) for the association [103], with poorly controlled hypertension being associated with higher psoriasis severity [103]. Importantly, despite their increased risk of cardiovascular mortality, psoriatic patients and cardiovascular risk factors were found to receive no treatment or less cardiologic medical therapy compared with controls without psoriasis. Notably, the European Society of Cardiology recommends that psoriatic patients be screened for cardiovascular diseases and that psoriasis severity be considered if one is uncertain on whether starting treatment for cardiovascular risk factors [104]. In particular, younger patients and patients with greater psoriasis severity deserve particular attention from clinicians as they are at highest risk. Other than medical treatment for cardiovascular risk factors, counselling to these patients is also important as dietary interventions and physical exercise were shown to have a positive effect on both the cardiovascular risk profile and psoriasis severity. Ultimately, treatment with biologic agents (including TNF α inhibitors) was found to reduce the risk of major cardiac events, coronary artery disease progression and to reduce vascular inflammation [104].

Another group of comorbidities associated with psoriasis are metabolic diseases. Psoriatic patients have a higher prevalence of overweight or obesity, and obesity, body mass index (BMI), hip circumference and waist-hip ratio were found to be all independent risk factors for psoriasis [103]. The association between obesity and psoriasis was confirmed by a meta-analysis which found a pooled OR of 1.66 for the association between the two diseases (95% CI 1.46–1.89) [103]. Of note, there appears to be a correlation between psoriasis severity and obesity [103]. Furthermore, psoriasis was shown to be an independent risk factor for type 2 diabetes mellitus, with patients with severe psoriasis being at highest risk [103]. Of note, micro- and macro-vascular complications are more frequent in diabetic patients with psoriasis compared with those without psoriasis. The association between psoriasis and diabetes was confirmed by a metanalysis which found a

pooled OR of 1.76 (95% CI 1.59–1.96) [103]. Dyslipidemia is likewise more common in psoriatic patients than in controls, with ORs ranging between 1.04 and 5.55 according to a systematic review [103]. Patients with severe psoriasis seem to be at higher risk of dyslipidemia. Metabolic syndrome – a clustering of cardiovascular risk factors, including central obesity, hypertension, insulin resistance, and dyslipidemia – was also found to be associated with psoriasis, with a pooled OR of 2.26 (95% CI 1.70–3.01) according to a meta-analysis [103]. The analysis of the separate conditions of metabolic syndrome showed that the strongest association was between obesity and psoriasis. Also, the prevalence of metabolic syndrome was found to be directly correlated with psoriasis body surface area [103]. Lastly, a few studies suggest that psoriasis may be associated with an increased prevalence of nonalcoholic fatty liver disease (NAFLD), a term that includes a spectrum of liver disorders ranging from mild hepatic steatosis to nonalcoholic steatohepatitis (NASH). In this regard, a meta-analysis found a pooled OR of 2.15 (95% CI, 1.57–2.94) [101]. As for metabolic syndrome, a positive correlation was found between psoriasis severity (measured using BSA) and mild liver disease [101].

Psoriasis was also found to be associated with an increased prevalence of IBD, particularly Crohn's disease, and with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Regarding the two latter conditions, patients with greater psoriasis severity seem to be at highest risk of CKD. Indeed, a cohort study found that severe psoriasis is a risk factor for CKD and ESRD independent of other risk factors (e.g. age, diabetes, hypertension, hyperlipidemia, etc.) with a hazard ratio of 1.93 (95% CI 1.79–2.08) for CKD and 4.15 (95% CI 1.70–10.11) for ESRD [101]. Furthermore, psoriasis is associated with an increased risk of cancer. In this regard, patients receiving treatments for severe psoriasis were found to have a 41% increase in the risk of dying from malignancy compared to subjects without psoriasis [101]. A meta-analysis found a standardized incidence ratio for the overall risk of cancer (excluding non-melanoma skin cancers) in psoriatic patients of 1.16 (95% CI 1.07–1.25) [101]. Among malignancies, lymphoma (and cutaneous T cell lymphoma in particular) was consistently associated with psoriasis. Of note, an increased risk of lymphoma (1.3 to 2-fold)

was found even in psoriatic patients without who had not been treated with immunosuppressants [101].

Psoriasis has also a remarkable psychological impact given the stigmatization experienced by patients, and is associated with psychiatric comorbidities such as anxiety and depression, which have a higher prevalence in psoriatic patients than in the general population. The prevalence of anxiety in psoriasis was reported by a systematic review to range from 7 to 48% [105], which is significantly higher than its prevalence in the global population (7.3%). Moreover, psoriatic patients are more likely to experience depression (OR 1.57, 95%CI 1.40-1.76) and use antidepressants (OR 4.24, 95%CI 1.53-11.76) [106]. Risk factors for the development of depression in these patients were reported to be female gender, early-onset psoriasis, longer disease duration, involvement of sensitive areas, and more severe disease. Lastly, the prevalence of suicidal ideation ranged from 0.4% to 21.0% across studies, a figure which is significantly higher than in controls [107].

Economic burden

Psoriasis has a remarkable economic impact on patients and healthcare systems. First, there are direct costs which include pharmacological (including biological) treatments, nonpharmacological treatments (including phototherapy), diagnostic tests, visits to the clinic, hospitalization, transport, rehabilitation. In the last decade, the introduction of biologic treatments has led to an increase in treatment costs; however, the availability of new, more effective treatments has allowed to significantly reduce hospitalizations. Secondly, there are indirect costs related to psoriasis such as loss of productivity, absence from work, early retirement, unemployment and occupational disability. Furthermore, comorbidities associated with psoriasis (such as psoriatic arthritis, mental health conditions, metabolic diseases) add up to the direct and indirect costs.

Regarding the direct and indirect costs of psoriasis (excluding comorbidities), a 2015 systematic review of the literature (conducted using the MEDLINE and EMBASE databases and the Consolidated Health Economic Evaluation Reporting Standards checklist to assess for methodological quality) assessed studies that

estimated the direct and/or indirect costs of psoriasis in the five largest European countries (Germany, Spain, France, Italy and the United Kingdom) [108]. The results of the review are summarized in Table 11 (prices have been adjusted to 2024 using the consumer price index [109]). Of note, studies that evaluated psoriasis costs in the United States have also been added to Table 11.

Table 11. Costs of psoriasis per patient per year in the five largest European countries and in the United States (including the original costs and costs adjusted to 2024). Modified from [108].

Country	Study (year)	Study population	Direct costs (original)	Indirect costs (original)	Total costs (original)	Direct costs (2024)	Indirect costs (2024)	Total costs (2024)
Italy	Finzi et al. (2001)[110]	Psoriasis (any subtypes and severity)	905€	NA	905€	1726€	NA	1726€
	Colombo, et al. (2008)[111]	Moderate psoriasis	3643€	1583€	5226€	5087€	2210€	7298€
		Severe psoriasis	7683€	3751€	11434€	10728€	5238€	15966€
France	Le Moigne et al. (2014)[112]	Pts on biologics	16214€	NA	16214€	20247€	NA	20247€
		Pts on conventional systemic agents or phototherapy	3356€	NA	3356€	4191€	NA	4191€
Spain	Carrascosa et al. (2006)[113]	PASI<10	775€	118€	893€	1234€	188€	1422€
		PASI 10-20	1028€	245€	1265€	1637€	390€	2014€
		PASI>20	1574€	595€	2169€	2506€	2506€	3453€
	Sanchez-Carazo et al. (2009)[114]	Moderate-to-severe psoriasis	6420€	461€	6881€	8691€	624€	9316€
Germany	Berger et al. (2005)[115]	Moderate-to-severe psoriasis	1426€	1440€	2866€	2214€	2236€	4449€
	Schöffski et al. (2007)[116]	Moderate-to-severe psoriasis	5397€	1310€	6707€	7908€	1919€	9827€
	Steinke et al. (2009)[117]	Inpatients	10070€	2973€	13042€	14755€	4356€	19109€
		Outpatients	2476€	509€	2985€	3628€	746€	4374€

United Kingdom	Fonia et al. (2010)[118]	Pts on biologics	4207£	NA	4207£	6646£	NA	6646£
		Pts on conventional systemic drugs	1891£	NA	1891£	2987£	NA	2987£
United States	Fowler et al. (2008)[119]	Psoriasis (any severity)	3960\$	1548\$	5508\$	6162\$	2409\$	8571\$
	Yu et al. (2009)[120]	Psoriasis (any severity)	5529\$	NA	5529\$	8365\$	NA	8365\$
		Mild psoriasis	5011\$	NA	5011\$	7581\$	NA	7581\$
		Moderate-to-severe psoriasis	10593\$	NA	10593\$	16026\$	NA	16026\$
	Gunnarsson et al. (2012) [121]	Psoriasis (any severity)	5802\$	NA	5802\$	8453\$	NA	8453\$
	Feldman et al. (2015)[122]	Moderate-to-severe psoriasis	13731\$	NA	13731\$	18760\$	NA	18760\$
	Al Sawah et al. (2017)[123]	Psoriasis (any severity)	12523\$	NA	12523\$	16594\$	NA	16594\$
		Moderate-to-severe psoriasis	21481\$	NA	21481\$	28464\$	NA	28464\$
		Psoriasis pts on biologics	29832\$	NA	29832\$	39529\$	NA	39529\$
		Psoriasis pts with PsA	23432\$	NA	23432\$	31049\$	NA	31049\$

NA: not available; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis.

In regard to direct costs, they are significantly higher for patients with increasing psoriasis severity due to higher treatment costs (including biological drugs), more frequent visits and laboratory exams, and the higher incidence of comorbidities. Psoriasis-related drug expenditure is the largest driver of healthcare costs in psoriasis. In this regard, biologic agents - while more effective and safer than conventional systemic agents – add tremendously to the economic burden of psoriasis. Of note, the direct costs in Table 11 might no longer be up-to-date as a few of the studies were conducted before the introduction of biologics while unfortunately no study has evaluated the direct total costs of psoriasis after the introduction of biosimilars.

In regard to indirect costs, these were 40% of the total costs in the United States [119], while in Europe they varied significantly across different countries. In a multinational study (including psoriatic patients from France, Germany, Spain, Italy, United Kingdom and United States), the United States had the highest annual indirect costs per patient due to work productivity loss (9591\$). Importantly, in that study the annual indirect costs per patient due to work

productivity loss were found to increase with psoriasis severity, ranging from 3592\$ for mild psoriasis, to 7478\$ and 12194\$ for moderate and severe psoriasis respectively [124].

Several comorbidities frequently accompany psoriasis [125], including psoriatic arthritis, depression, anxiety, IBDs, diabetes, obesity, non-alcoholic fatty liver disease and cardiovascular diseases, which add to disease burden [126]. Such comorbidities contribute greatly to the economic burden of psoriasis as they result in increased direct and indirect healthcare costs. A few studies (all of which were conducted in the United States) have assessed the economic burden of comorbidities in patients with psoriasis and are summarized in Table 12.

Table 12. Economic burden of the comorbidities associated with psoriasis.

Study (year)	Comorbidities assessed	Main findings
Kimball et al. (2011)[127]	Any comorbidities	Psoriatic pts with comorbidities had an adjusted direct cost difference (vs psoriatic pts without comorbidities) during the 6-month study period of 2184\$
Feldman et al. (2017)[128]	Any comorbidities	Annual adjusted <i>direct</i> cost differences in psoriatic pts with PsA, peripheral vascular disease, and cardiovascular disease (vs psoriatic pts without comorbidities) were \$9914.3, \$8386.5 and \$8275.1 respectively <i>Indirect</i> annual cost differences for cerebrovascular disease, obesity, peripheral vascular disease and depression (vs psoriatic pts without comorbidities) were \$1333, \$1195, \$994.9 and \$996.6 respectively
Feldman et al. (2015)[129]	Psoriatic arthritis	Patients with moderate-to-severe psoriasis and comorbid PsA had annual direct costs of 27123\$ (adjusted cost difference vs controls without psoriasis: 23160\$)
Cai et al. (2019)[130]	Anxiety and depression	Annual unadjusted incremental direct costs associated with anxiety/depression in psoriatic patients were 8077\$
Pilon et al. (2019)[131]	Any comorbidities	Psoriasis pts with 0, 1-2 and ≥ 3 comorbidities had an annual <i>direct</i> cost difference (vs non-psoriasis pts) of 1590\$, 5870\$ and 18427\$ and an annual <i>indirect</i> cost difference of 335\$, 655\$ and 1695\$

PsA: psoriatic arthritis.

Aim of the study

The treatment of moderate-to-severe psoriasis has been revolutionized by biological drugs (including TNF- α , IL-17, IL-12/23 and IL-23 inhibitors). Despite their excellent efficacy and safety, their high cost still represents a major hindrance to a wider and early use. In the last few years, however, the expiration of the patents of TNF- α inhibitors has allowed the development of biosimilar versions of these agents. Currently, biosimilars of three TNF- α inhibitors are available: adalimumab, etanercept and infliximab. While the use of biosimilars is associated with significant reductions in drug costs [133], price variability across Europe of the biosimilar agents used in psoriasis has not been studied yet. The aim of this study was therefore to investigate the price variability across European countries of the currently available biosimilar agents for psoriasis, i.e. TNF- α inhibitor biosimilars of adalimumab, etanercept and infliximab.

MATERIALS AND METHODS

A survey was conducted of five dermatologists working at academic reference centres for psoriasis in Denmark (Aarhus), France (Toulouse), Germany (Lübeck), Italy (Verona) and Spain (Barcelona). The dermatologists were selected on the basis of their internationally recognized expertise in the treatment of psoriasis. Dermatologists were requested to provide the discounted net price (excluding value added tax, i.e. VAT) of one package of adalimumab, etanercept and infliximab originator and biosimilars paid by their local hospital pharmacies. Along with the originators (Humira[®], Abbvie; Enbrel[®], Amgen; Remicade[®], Janssen Biotech), the following biosimilars were included in the survey: for adalimumab, Amgevita[®] (Amgen), Hulio[®] (Mylan), Hyrimoz[®] (Sandoz), Idacio[®]

(Fresenius Kabi) and Imraldi® (Biogen); for etanercept, Benepali® (Biogen) and Erelzi® (Sandoz); for infliximab, Flixabi® (Samsung Bioepis), Inflectra® (Pfizer), Remsima® (Celltrion Healthcare) and Zessly® (Sandoz). The following package format was considered for each drug: for adalimumab, one package with two 40 mg subcutaneous (S.C.) syringes/autoinjectors; for etanercept, one package with four 50 mg subcutaneous syringes/autoinjectors; for infliximab, one package with one 100 mg intravenous (I.V.) vial - except for Remsima® for which one package with either one 100 mg intravenous vial or one 120 mg subcutaneous syringe was surveyed, depending on local availability. All prices were reported in 2023 Euros. Data were collected by email on a shared Excel sheet (Supplementary Files). Furthermore, ex-factory list prices of the originator before loss of exclusivity (excluding VAT) were obtained from the literature [134-137] and from the Italian Medicine Agency AIFA (Agenzia Italiana del Farmaco) [138-140]. Based on the prices per package, the price per unit dose (i.e. the amount of medication administered to a patient in a single dose) was then calculated. For infliximab, the unit dose was considered either 400 mg (corresponding to 5 mg/kg considering a patient weight of 80 kg) for I.V. vials or one S.C. 120 mg syringe. Furthermore, the following other costs were calculated: monthly maintenance regimen cost (at steady state), annual cost of treatment (including induction), price per milligram (mg), and percentual discount on the price of a unit dose of originator and its biosimilars in 2023 compared to the originator price before loss of exclusivity. The variability of the price of biosimilars across the selected European countries was assessed by calculating the difference between minimum and maximum price per unit dose. The price difference (as a percentage) compared to the originator for each biosimilar was also calculated.

RESULTS

Drug prices per unit dose of adalimumab, etanercept and infliximab originator and biosimilars are reported in Tables 13a, 14a and 15a and in Figures 1, 3 and 5. Unfortunately, German net discounted prices could not be obtained because discounts are confidential and cannot be made publicly available in Germany, hence ex-factory list prices were reported. Regarding adalimumab, the highest

price per unit dose of biosimilars was reported in Germany (Amgevita[®], €494.51) while the lowest in Spain (Idacio[®], €21.00; Table 13a). Overall, the prices per unit dose of adalimumab biosimilars were highest in Germany (€488.38-494.51), lowest in Spain (€21.00-27.06) and Italy (€23.60-41.58) while in France and Denmark prices laid in between (€234.50 for France and €202.94-210.70 for Denmark). As for etanercept, the highest price per unit dose of biosimilars was also reported in Germany (Benepali[®], €282.52) and the lowest in Italy (Erelzi[®], €11.69; Table 14a). Overall, prices per unit dose of etanercept biosimilars were highest in Germany and lowest in Italy (€11.69) and Spain (€48.00-63.00) while French prices (€131.00) were between those of Germany and Spain. Regarding infliximab, the highest price per unit dose of biosimilars was reported again in Germany (S.C. Remsima[®], €716.45) whereas the lowest in Spain (I.V. Zessly[®], €191.60; Table 15a). Overall, German prices per unit dose of infliximab were the highest while Spanish ones were the lowest (ranging from €191.60 to 232.00); prices in Italy and France were similar and both slightly higher than the Spanish ones (€224.40-519.20 for Italy, €241.00-528.00 for France). No data on etanercept and infliximab prices were available from Denmark.

Among adalimumab biosimilars, Idacio[®] had the largest difference in drug prices per unit dose across European countries (€23.60 in Italy vs €488.38 in Germany) while among etanercept biosimilars the largest difference in drug prices per unit dose was reported for Benepali[®] (€48 in Spain vs €282.52 in Germany) and among infliximab biosimilars (considering only the I.V. formulation) for Flixabi[®] (€232 in Spain vs €528 in France).

Compared to the originator price at the time of the study (*in 2023*), adalimumab biosimilar prices per unit dose were 33.5-35.9% lower in Denmark, 15.8% lower in France, 70.9-83.5% lower in Italy and 65.5-73.2% lower in Spain. As to etanercept, biosimilar prices per unit dose were the same as the originator in Germany, 2.1% lower than the originator in France, 70.2% in Italy and 62.7-71.6% in Spain. Lastly, infliximab biosimilars had the same price per unit dose of the originator in France – with the exception of subcutaneous Remsima[®] which was 47.8% cheaper, albeit with a different dosing – while they were 55.1-80.6% cheaper than the originator in Italy and 75.3-79.6% in Spain.

Compared to the originator price *before loss of exclusivity*, the highest percentual discounts for adalimumab biosimilars were reported in Italy (95.58% for Idacio[®]) and Spain (95.75% for Idacio[®]; Table 13b, Figure 2). Overall, there was a great variability in discounts across countries: percentual discounts of adalimumab biosimilars were low in Germany (36.10-36.90%), very high in Italy and Spain (92.22-95.58% and 94.52-95.75% respectively) and intermediate in Denmark (59.36-60.37%) and France (54.33%). For etanercept the highest percentual discount on biosimilars compared to the originator price before loss of exclusivity (Table 14b, Figure 4) was reported in Italy (95.42% for Erelzi[®]). Overall, there was high variability in discount across countries, with percentual discounts on etanercept biosimilars being highest in Italy (95.42%), intermediate in Spain (72.27-78.74%) and lowest in France (48.05%) and Germany (18.43%). For infliximab biosimilars (Table 15b, Figure 6), the highest percentual discounts were reported in Italy (90.72% for Zessly[®]) and Spain (90.02%, also for Zessly[®]). Overall, the variability in discounts was lower than for etanercept and adalimumab. In detail, percentual discounts on infliximab biosimilars were lowest in Germany (69.73%) and highest in Spain (88.76-90.72%) while in Italy and France they laid in between (77.26-90.02% and 76.47-89.26% respectively).

Further data on monthly maintenance costs, annual costs of treatment and prices per milligram of the originator and biosimilars of adalimumab, etanercept and infliximab are reported in Tables 13c,d,e, 14c,d,e and 15c,d,e respectively. In particular, the monthly cost treatment with adalimumab biosimilar Idacio[®] in Italy and Spain was as low as €47.20 and €42.00, respectively (Table 13c). In contrast, monthly treatment with adalimumab biosimilars in France and Denmark was eight- to ten-times as expensive (€469.00 in France and €405.88-421.40 in Denmark), and even more expensive in Germany (€976.76-989.02, Table 13c). Considering the annual cost of treatment with adalimumab biosimilars, it was mostly under €1000 in Italy and Spain (with the exception of Amgevita[®] in Italy), with the least expensive being Idacio[®] (€672.60 and €598.50 in Italy and Spain, respectively, Table 13d). In contrast, it was €5783.79-6004.95 in Denmark, €6683.25 in France and over €10000 (in detail, €13918.83-14093.54) in Germany (Table 13d). Treating a psoriasis patient with the lowest-price adalimumab

biosimilar for a year compared with treatment with the originator would lead to annual savings of €3402.90 in Italy, €3244.44 in Denmark, €1635.33 in Spain and €1254.00 in France.

Regarding etanercept biosimilars, the monthly cost of treatment was lowest in Italy (€46.76-157.08), slightly higher in Spain (€192-252) and markedly higher in France (€524) and Germany (€1130.08, Table 14c). Considering the annual cost of treatment with etanercept biosimilars, it was under €1000 only for Erelzi® in Italy (€748.16), while it was €3072-4032 in Spain, €8348 in France and above €10000 in Germany (in detail, €18081.28; Table 14d). Treating a psoriasis patient with the lowest-price etanercept biosimilar for a year compared with treatment with the originator would lead to annual savings of €7748.48 in Spain and €1765.12 in Italy while it had the same annual cost of the originator in Germany and almost the same cost in France (annual savings using biosimilars were only €176).

Regarding infliximab, the monthly cost of treatment was lowest in Spain (€95.80-116.00), slightly higher in Italy (€112.20-259.60) and highest in France (€264.00-482) and Germany (€1432.90; Table 15c). Similarly, considering the annual cost of treatment with infliximab biosimilars, it was lowest in Spain (€1484.90-1798.00), slightly higher in Italy and France (€1739.10-4023.80 in Italy, €1867.75-4092 in France) and highest in Germany (in detail, €5552.49; Table 15d). Treating a psoriasis patient with the lowest-price I.V. infliximab biosimilar for a year compared with treatment with the originator would lead to annual savings of €7216.49 in Italy and €5788.63 in Italy while it had the same annual cost of the originator in in France.

Table 13a. Drug price per unit dose of adalimumab originator before loss of exclusivity and of the originator and its biosimilars in 2023 in selected European countries (in Euro). The unit dose considered was 40 mg syringe/auto-injector.

Prices do not include VAT.

	HUMIRA® (pre-loss of exclusivity)	HUMIRA® (2023)	AMGEVITA® (2023)	HULIO® (2023)	HYRIMOZ® (2023)	IDACIO® (2023)	IMRALDI® (2023)
Germany (Lübeck)	773.93*	NA	488.38- 494.51*	NA	488.38*	488.38*	488.55*
Denmark (Aarhus)	518.40*	316.78^	205.44^	NA	210.70^	NA	202.94^
France (Toulouse)	513.45*	278.50^	234.50	234.50^	234.50^	234.50^	234.50^
Italy (Verona)	534.28*	143.00^	41.58^	NA	23.76^	23.60^	24.83^
Spain (Barcelona)	494.61*	78.38^	27.06^	NA	27.00^	21.00^	25.00^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Table 13b. Percentual discount on the price of a unit dose of adalimumab originator and its biosimilars in 2023 compared to the originator price before loss of exclusivity in selected European countries (in Euro). The unit dose considered was 40 mg syringe/auto-injector.

	HUMIRA® (pre-loss of exclusivity)	HUMIRA® (2023)	AMGEVITA® (2023)	HULIO® (2023)	HYRIMOZ® (2023)	IDACIO® (2023)	IMRALDI® (2023)
Germany (Lübeck)	-	NA	36.90-36.10%	NA	36.90%	36.90%	36.87%
Denmark (Aarhus)	-	38.89%	60.37%	NA	59.36%	NA	60.85%
France (Toulouse)	-	45.76%	54.33%	54.33%	54.33%	54.33%	54.33%
Italy (Verona)	-	73.24%	92.22%	NA	95.55%	95.58%	95.35%
Spain (Barcelona)	-	84.15%	94.52%	NA	94.54%	95.75%	94.95%

NA: not available

Table 13c. Monthly maintenance regimen cost (steady state) of adalimumab (40 mg syringe/auto-injector) originator before loss of exclusivity and with the originator and its biosimilars in 2023 in selected European countries (in Euro). Prices do not include VAT.

	HUMIRA® (pre-loss of exclusivity)	HUMIRA® (2023)	AMGEVITA® (2023)	HULIO® (2023)	HYRIMOZ® (2023)	IDACIO® (2023)	IMRALDI® (2023)
Germany (Lübeck)	1547.86*	NA	976.76- 989.02*	NA	976.76*	976.76*	977.10*
Denmark (Aarhus)	1036.80*	633.56^	410.88^	NA	421.40^	NA	405.88^
France (Toulouse)	1026.90*	557.00^	469.00^	469.00^	469.00^	469.00^	469.00^
Italy (Verona)	1068.56*	286.00^	83.16^	NA	47.52^	47.20^	49.66^
Spain (Barcelona)	989.22*	156.76^	54.12^	NA	54.00^	42.00^	50.00^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Table 13d. Annual cost of treatment (including induction) of adalimumab (40 mg syringe/auto-injector) originator before loss of exclusivity and with the originator and its biosimilars in 2023 in selected European countries (in Euro). Prices do not include VAT.

	HUMIRA® (pre- loss of exclusivity)	HUMIRA® (2023)	AMGEVITA® (2023)	HULIO® (2023)	HYRIMOZ® (2023)	IDACIO® (2023)	IMRALDI® (2023)
Germany (Lübeck)	22057.01*	NA	13918.83- 14093.54*	NA	13918.83*	13918.83*	13923.68*
Denmark (Aarhus)	14774.40*	9028.23^	5855.04^	NA	6004.95^	NA	5783.79^
France (Toulouse)	14633.33*	7937.25^	6683.25^	6683.25^	6683.25^	6683.25^	6683.25^
Italy (Verona)	15226.98*	4075.50^	1185.03^	NA	677.16^	672.60^	707.66^
Spain (Barcelona)	14096.39*	2233.83^	771.21^	NA	769.50^	598.50^	712.50^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Table 13e. Price per milligram (mg) of adalimumab (assuming treatment with 40 mg syringe/auto-injector) originator before loss of exclusivity and with the originator and its biosimilars in 2023 in selected European countries (in Euro). Prices do not include VAT.

	HUMIRA® (pre-loss of exclusivity)	HUMIRA® (2023)	AMGEVITA® (2023)	HULIO® (2023)	HYRIMOZ® (2023)	IDACIO® (2023)	IMRALDI® (2023)
Germany (Lübeck)	19.35*	NA	12.21-12.36*	NA	12.21*	12.21*	12.21*
Denmark (Aarhus)	12.96*	7.92^	5.14^	NA	5.27^	NA	5.07^
France (Toulouse)	12.84*	6.96^	5.86^	5.86^	5.86^	5.86^	5.86^
Italy (Verona)	13.36*	3.58^	1.04^	NA	0.59^	0.59^	0.62^
Spain (Barcelona)	12.37*	1.96^	0.68^	NA	0.68^	0.53^	0.63^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Figure 1. Drug price per unit dose of adalimumab originator before loss of exclusivity and of the originator and its biosimilars in 2023 in selected European countries (in Euro). The unit dose considered was 40 mg syringe/auto-injector. Prices do not include VAT.

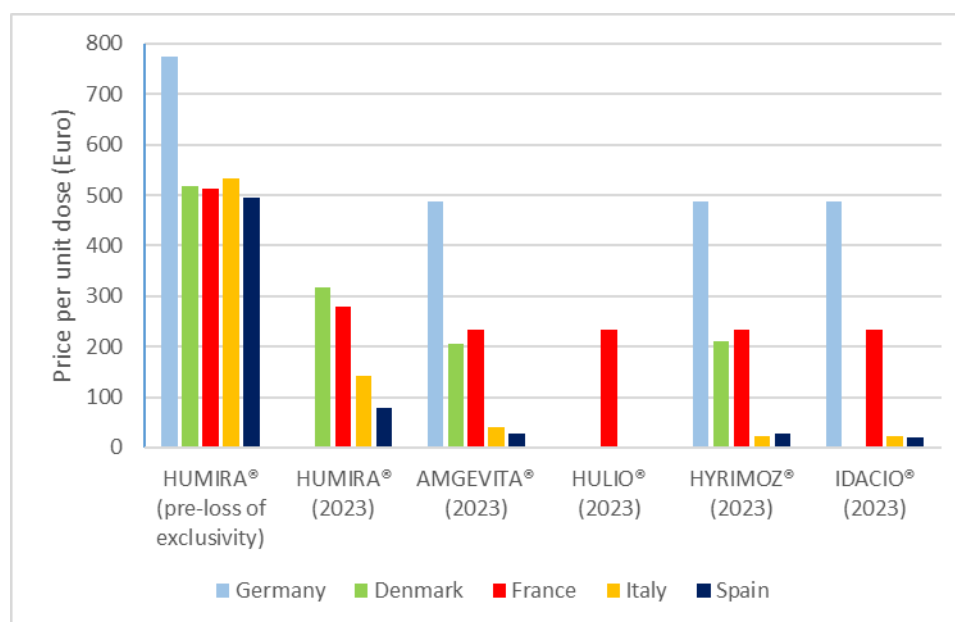


Figure 2. Percentual discount on the price of a unit dose of adalimumab originator and its biosimilars in 2023 compared to the originator price before loss of exclusivity in selected European countries (in Euro). The unit dose considered was 40 mg syringe/auto-injector.

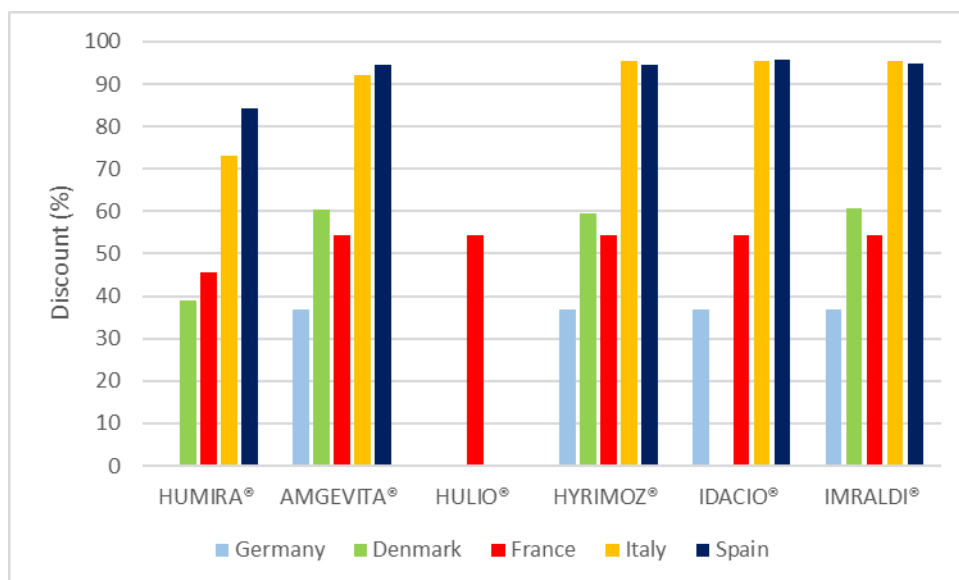


Table 14a. Drug price per unit dose of etanercept originator before loss of exclusivity and of the originator and its biosimilars in 2023 in selected European countries (in Euro). The unit dose considered was 50 mg syringe/auto-injector. Prices do not include VAT.

	ENBREL® (pre-loss of exclusivity)	ENBREL® (2023)	BENEPALI® (2023)	ERELZI® (2023)
Germany (Lübeck)	346.37*	282.52*	282.52*	NA
France (Toulouse)	252.16*	133.75^	131.00^	131.00^
Italy (Verona)	255.13*	39.27^	NA	11.69^
Spain (Barcelona)	227.21*	169.07^	48.00^	63.00^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Table 14b. Percentual discount on the price of a unit dose of etanercept originator and its biosimilars in 2023 compared to the originator price before loss of exclusivity in selected European countries (in Euro). The unit dose considered was 50 mg syringe/auto-injector.

	ENBREL® (pre-loss of exclusivity)	ENBREL® (2023)	BENEPALI® (2023)	ERELZI® (2023)
Germany (Lübeck)	-	18.43%	18.43%	NA
France (Toulouse)	-	46.96%	48.05%	48.05%
Italy (Verona)	-	69.22%	NA	95.42%
Spain (Barcelona)	-	25.59%	78.74%	72.27%

Table 14c Monthly maintenance regimen cost (steady state) of etanercept (50 mg syringe/auto-injector) originator before loss of exclusivity and with the originator and its biosimilars in 2023 in selected European countries (in Euro). Prices do not include VAT.

	ENBREL® (pre-loss of exclusivity)	ENBREL® (2023)	BENEPALI® (2023)	ERELZI® (2023)
Germany (Lübeck)	1385.48*	1130.08*	1130.08*	NA
France (Toulouse)	1108.64*	535.00^	524.00^	524.00^
Italy (Verona)	1020.52*	157.08^	NA	46.76^
Spain (Barcelona)	908.84*	676.28^	192.00^	252.00^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Table 14d. Annual cost of treatment (including induction) of etanercept (50 mg syringe/auto-injector) originator before loss of exclusivity and with the originator and its biosimilars in 2023 in selected European countries (in Euro). Prices do not include VAT.

	ENBREL® (pre-loss of exclusivity)	ENBREL® (2023)	BENEPALI® (2023)	ERELZI® (2023)
Germany (Lübeck)	22167.68*	18081.28*	18081.28*	NA
France (Toulouse)	16138.24*	8560.00^	8384.00^	8384.00^
Italy (Verona)	16328.32*	2513.28^	NA	748.16^
Spain (Barcelona)	14541.44*	10820.48^	3072.00^	4032.00^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Table 14e. Price per milligram (mg) of etanercept (assuming treatment with 50 mg syringe/auto-injector) originator before loss of exclusivity and with the originator and its biosimilars in 2023 in selected European countries (in Euro). Prices do not include VAT.

	ENBREL® (pre-loss of exclusivity)	ENBREL® (2023)	BENEPALI® (2023)	ERELZI® (2023)
Germany (Lübeck)	6.93*	5.65*	5.65*	NA
France (Toulouse)	5.04*	2.68^	2.62^	2.62^
Italy (Verona)	5.10*	0.79^	NA	0.23^
Spain (Barcelona)	4.54*	3.38^	0.96^	1.26^

NA: not available. *Ex-factory (list) price. ^Discounted net price

Figure 3. Drug price per unit dose of etanercept originator before loss of exclusivity and of the originator and its biosimilars in 2023 in selected European countries (in Euro). The unit dose considered was 50 mg syringe/auto-injector. Prices do not include VAT.

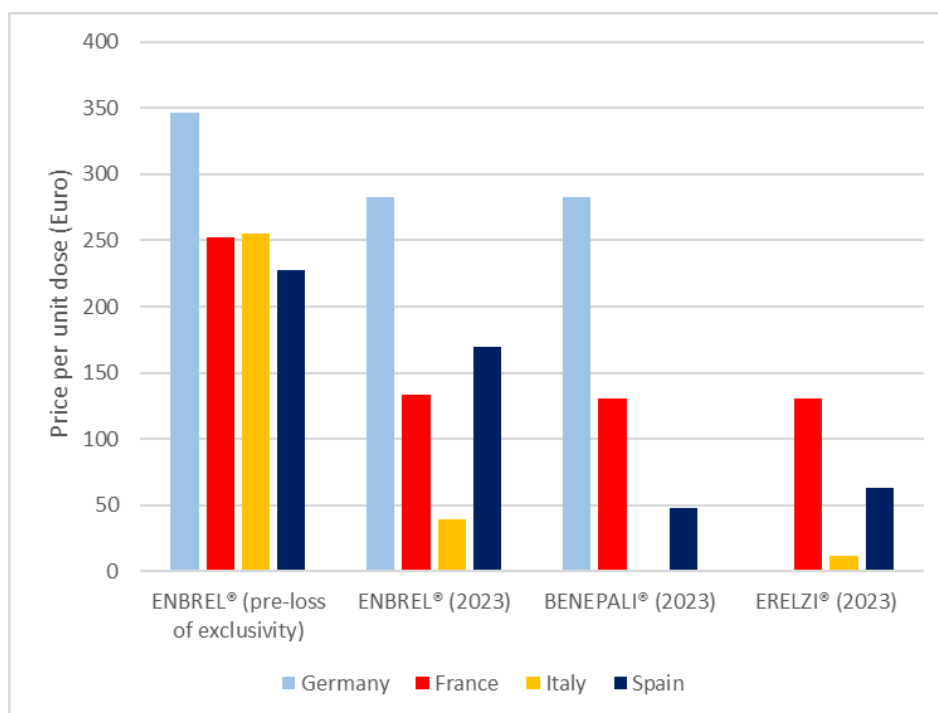


Figure 4. Percentual discount on the price of a unit dose of etanercept originator and its biosimilars in 2023 compared to the originator price before loss of exclusivity in selected European countries (in Euro). The unit dose considered was 50 mg syringe/auto-injector.

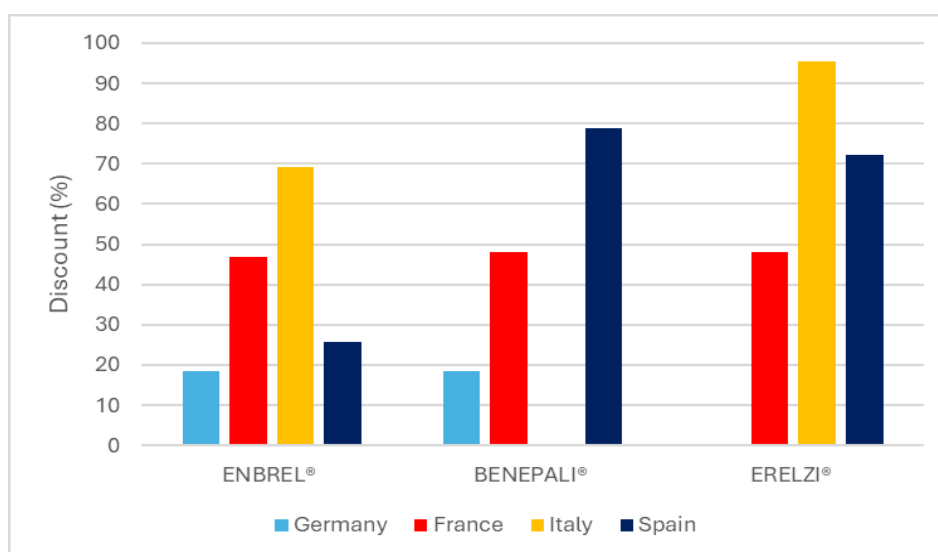


Table 15a. Drug price per unit dose of infliximab originator before loss of exclusivity and of the originator and its biosimilars in 2023 in selected European countries (in Euro). The unit dose considered was either 400 mg for I.V. vials or one S.C. 120 mg syringe. Prices do not include VAT.

	REMICADE® I.V. (pre-loss of exclusivity)	REMICADE® I.V. (2023)	FLIXABI® I.V. (2023)	INFLECTRA® I.V. (2023)	REMSIMA® I.V. (2023)	REMSIMA® S.C. (2023)	ZESSLY® I.V. (2023)
Germany (Lübeck)	2366.72*	NA	NA	NA	NA	716.45*	NA
France (Toulouse)	2244.00*	528.00^	528.00^	528.00^	NA	241.00^	NA
Italy (Verona)	2282.72*	1155.56^	NA	519.20^	285.92^	NA	224.40^
Spain (Barcelona)	2063.60*	938.52^	232.00^	NA	220.00^	NA	191.60^

NA: not available; I.V.: intravenous; S.C.: subcutaneous *Ex-factory (list) price. ^Discounted net price

Table 15b. Percentual discount on the price of a unit dose of infliximab originator and its biosimilars in 2023 compared to the originator price before loss of exclusivity in selected European countries (in Euro). The unit dose considered was either 400 mg for I.V. vials or one S.C. 120 mg syringe.

	REMICADE® I.V. (pre-loss of exclusivity)	REMICADE® I.V. (2023)	FLIXABI® I.V. (2023)	INFLECTRA® I.V. (2023)	REMSIMA® I.V. (2023)	REMSIMA® S.C. (2023)	ZESSLY® I.V. (2023)
Germany (Lübeck)	-	NA	NA	NA	NA	69.73%	NA
France (Toulouse)	-	76.47%	76.47%	76.47%	NA	89.26%	NA
Italy (Verona)	-	49.38%	NA	77.26%	87.47%	NA	90.02%
Spain (Barcelona)	-	54.52%	88.76%	NA	89.34%	NA	90.72%

NA: not available; I.V.: intravenous; S.C.: subcutaneous

Table 15c. Monthly maintenance regimen cost (steady state) of infliximab (400 mg I.V.) originator before loss of exclusivity and of the originator and its biosimilars (400 mg I.V. or 120 mg S.C.) in 2023 in selected European countries (in Euro). Prices do not include VAT.

	REMICADE® I.V. (pre-loss of exclusivity)	REMICADE® I.V. (2023)	FLIXABI® I.V. (2023)	INFLECTRA® I.V. (2023)	REMSIMA® S.C. (2023)	REMSIMA® S.C. (2023)	ZESSLY® I.V. (2023)
Germany (Lübeck)	1183.36*	NA	NA	NA	NA	1432.90*	NA
France (Toulouse)	1122.00*	264.00^	264.00^	264.00^	NA	482.00^	NA
Italy (Verona)	1141.36*	577.78^	NA	259.60^	142.96^	NA	112.20^
Spain (Barcelona)	1031.80*	469.26^	116.00^	NA	110.00^	NA	95.80^
NA: not available; I.V.: intravenous; S.C.: subcutaneous *Ex-factory (list) price. ^Discounted net price							

Table 15d. Annual cost of treatment (including induction) of infliximab (400 mg I.V.) originator before loss of exclusivity and with the originator and its biosimilars (400 mg I.V. or 120 mg S.C.) in 2023 in selected European countries (in Euro). Prices do not include VAT.

	REMICADE® I.V. (pre-loss of exclusivity)	REMICADE® I.V. (2023)	FLIXABI® I.V. (2023)	INFLECTRA® I.V. (2023)	REMSIMA® S.C. (2023)	REMSIMA® S.C. (2023)	ZESSLY® I.V. (2023)
Germany (Lübeck)	18342.08*	NA	NA	NA	NA	5552.49*	NA
France (Toulouse)	17391.00*	4092.00^	4092.00^	4092.00^	NA	1867.75^	NA
Italy (Verona)	17691.08*	8955.59^	NA	4023.80^	2215.88^	NA	1739.10^
Spain (Barcelona)	15992.90*	7273.53^	1798.00^	NA	1705.00^	NA	1484.90^
NA: not available; I.V.: intravenous; S.C.: subcutaneous *Ex-factory (list) price. ^Discounted net price							

Table 15e. Price per milligram (mg) of infliximab originator before loss of exclusivity and with the originator and its biosimilars (assuming treatment with 400 mg I.V. or 120 mg S.C.) in 2023 in selected European countries (in Euro). Prices do not include VAT.

	REMICADE® I.V. (pre-loss of exclusivity)	REMICADE® I.V. (2023)	FLIXABI® I.V. (2023)	INFLECTRA® I.V. (2023)	REMSIMA® I.V. (2023)	REMSIMA® S.C. (2023)	ZESSLY® I.V. (2023)
Germany (Lübeck)	5.92*	NA	NA	NA	NA	5.97*	NA
France (Toulouse)	5.61*	1.32^	1.32^	1.32^	NA	2.01^	NA
Italy (Verona)	5.71*	2.89^	NA	1.30^	0.71 ^α	NA	0.56^
Spain (Barcelona)	5.16*	2.35^	0.58^	NA	0.55 ^α	NA	0.48^

NA: not available; I.V.: intravenous; S.C.: subcutaneous *Ex-factory (list) price. ^Discounted net price

Figure 5. Drug price per unit dose of infliximab originator before loss of exclusivity and of the originator and its biosimilars in 2023 in selected European countries (in Euro). The unit dose considered was 400 mg for I.V. vials (for clarity, S.C. syringes are not included). Prices do not include VAT.

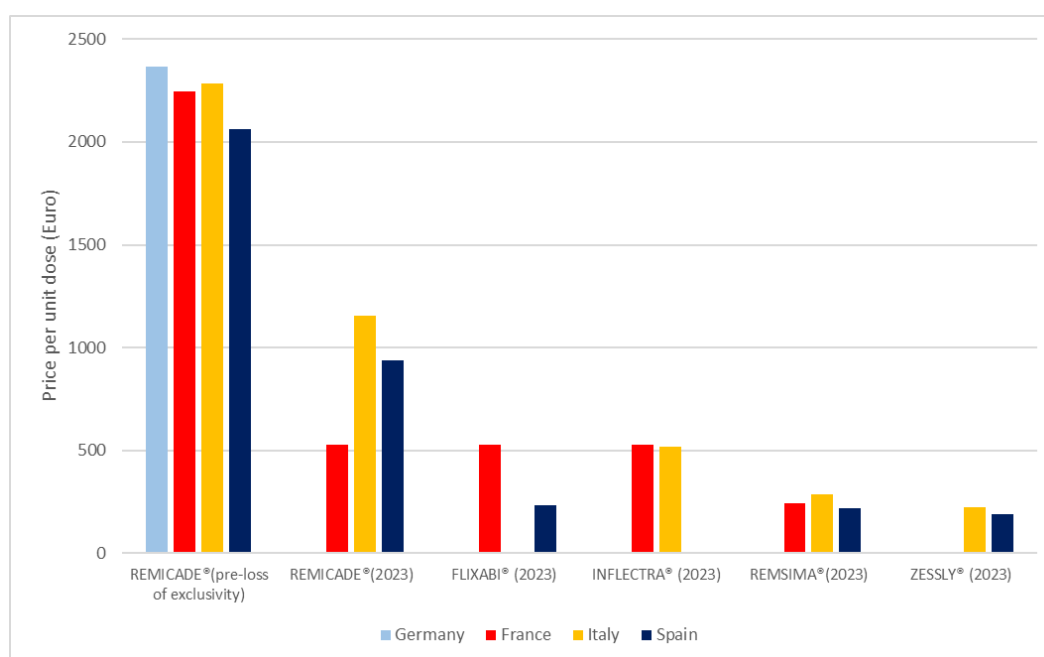
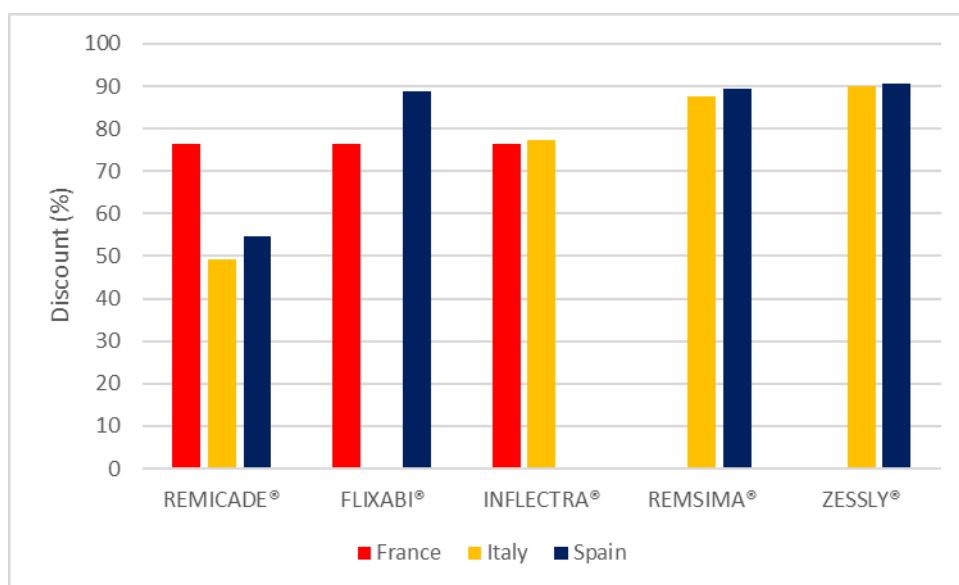


Figure 6. Percentual discount on the price of a unit dose of infliximab originator and its biosimilars in 2023 compared to the originator price before loss of exclusivity in selected European countries (in Euro). The unit dose considered was 400 mg for I.V. vials (for clarity, S.C. syringes are not included). Prices do not include VAT.



DISCUSSION

The main finding of this survey is that there is significant price variability of TNF- α inhibitor biosimilars across European countries, with drug prices in Italy and Spain being lower than in Germany, France and Denmark, both in absolute terms and relatively to the cost of the originator. Of note, a caveat applies to the German prices, as discounts in Germany among insurances, pharmacies, hospitals and producers (pharma) are not publicly available and transparent. Hence, the prices reported in this study represent pharmaceutical list prices, because biosimilar discounted prices in Germany cannot be available even to physicians. Insurance companies may have separate contracts with manufacturers with a discount for their insured patients. Furthermore, TNF- α inhibitor biosimilars are provided by hospital pharmacies in Germany only to patients treated in the hospital as inpatients, not to outpatients.

Although German *biosimilar* prices reported in this survey (which as stated above are ex-factory list prices) are not directly comparable with other countries' discounted biosimilar prices, when one compares Italian *ex-factory* prices of the biosimilar agents included in this study (which can be obtained from AIFA [141-145]) with the analogous German biosimilar ex-factory prices, the latter are higher for all agents included in the present study. For example, the ex-factory price (excluding VAT) of a unit dose of adalimumab biosimilars Hyrimoz[®], Idacio[®] and Imraldi[®] in Germany ranged between 488.38 and 488.55 Euro (Table 12). By contrast, in Italy the ex-factory price was 379.34 Euro for all (i.e. 22.3% lower)[141-143]. For etanercept biosimilar Benepali[®], the ex-factory price of a unit dose in Germany was 282.52 Euro (Table 13) as opposed to 174.24 Euro in Italy (i.e. 38.3% lower) [144]. For subcutaneous infliximab biosimilar Remsima[®], the ex-factory price of a unit dose (120 mg) in Germany was 716.45 Euro as opposed to 320.20 Euro in Italy (i.e. 55.3% lower)[145].

The price variability found in this study may be explained by the different pricing policies adopted by different European countries with regard to biosimilars [99]. Indeed, the most frequent biosimilar pricing mechanisms include mandatory discounts applied at launch, progressive price discounts applied over time and additional discounts negotiated through tendering or direct contracting with providers [146]. In most European countries, no single pricing mechanism is adopted but multiple pricing mechanisms are combined, both at national and local level [146]. For example, France adopts progressive mandatory discounts, multi-winner tenders are used in Germany, the United Kingdom, Italy and Spain (in addition to mandatory discounts in the latter two countries) and single winner tenders are used in Denmark. Indeed, in the present survey TNF- α inhibitor biosimilars were up to 83.5% cheaper than the originator, highlighting the effectiveness of tendering in achieving high price reductions through competition. Importantly, as tenders are managed both a national and at a regional level, regional price variation ensues both nationally and across European countries as shown by the present survey. This was confirmed by a web survey of hospital pharmacists and purchasers, which found considerable variations in the organization and design of tenders for off-patent biologics and biosimilars across

European countries [147]. In the survey, the need to optimize tender processes was expressed, with the aim of ensuring market plurality and including award criteria beyond price [147].

Another finding of this study is that, thanks to biosimilars, biological treatment of psoriasis is becoming increasingly sustainable across Europe - approaching the cost of treatment with conventional systemic agents [148,149]. For example, the price of one month of psoriasis treatment with Idacio® biosimilar adalimumab treatment in Italy assessed in this survey was as low as €47.19. By comparison, the cost of one month of therapy with 15 mg/week generic subcutaneous methotrexate in Italy is currently €40.52 [150]. Such price reduction in TNF- α inhibitor biosimilar prices achieved over the last few years in Europe is a major advancement in psoriasis treatment given that the high costs of biologics has long represented a serious obstacle to their wider use. Indeed, the introduction of biologics has led to a 3-fold to 5-fold increase in direct costs of the management of psoriasis in Europe [151]. Unsurprisingly, 19–24% of dermatologists considered costs to represent a barrier to the use of biologic therapy in psoriasis in a multinational survey conducted in Europe and Canada [152]. The introduction of biosimilars was associated with remarkable cost savings. For example, a budget impact model conducted in five European countries found that the introduction of infliximab biosimilar Remsima® alone would lead to annual cost savings ranging from €2.89 million (Belgium) to €33.80 million (Germany) [153]. Similarly, considerable cost savings were found in a British budget impact analysis following the introduction of TNF- α inhibitor biosimilars in the UK [154,155]. Indeed, a cost-effectiveness model which assessed the optimal biological treatment for moderate-to-severe psoriasis in the UK found the optimal first-line treatment to be adalimumab biosimilar [156]. Considering all biosimilars, a Spanish budget impact analysis estimated that cost savings from the payer perspective would reach €2306 million over 11 years [157].

Importantly, cost savings associated with the introduction of biosimilars may derive both from the reallocation of market shares from the originator to biosimilars and from price competition on originator prices induced by biosimilars. Indeed, an Italian budget impact analysis on a rituximab biosimilar

found that price competition on originators was the most relevant factor, accounting for 67% of the savings [158]. Hence, in order to compare the cost savings derived from the introduction of biosimilars across different countries, one should evaluate the originator's share and the different mix of biosimilars used in each country. Notably, in countries where multi-winner tenders are used for the procurement of biosimilars, different biosimilars are available for the same molecule (often with different prices) and the prescribed mix certainly varies across different countries.

Furthermore, when analyzing the cost savings associated with TNF- α inhibitor biosimilars, it must be taken into account that there is some degree of substitutability between the molecules considered (infliximab, etanercept, adalimumab). In this regard, a German study that assessed market dynamics of TNF α inhibitor originators and biosimilars from 2010 to 2018 found that, while there was an increased use of etanercept and infliximab after biosimilar entry, the compound annual growth rate of sales volume intensified for etanercept but decreased for infliximab [93]. Indeed, infliximab may have been subject to the competitive pressure of other TNF- α inhibitors which have the advantage of the subcutaneous administration.

Another important topic related to biosimilar prices is the impact of prices on the access to biological treatment. The cost savings derived from the introduction of biosimilar have been used in several European countries to allow more patients to receive biological treatment. In England, a study found that the number of patients prescribed biological or small molecule targeted treatments from 2019 to 2024 increased by 62% (from 4.11 to 6.64 people per 1000) without increase in drug spending [159]. Of note, in the 3 years that followed the introduction of adalimumab biosimilars, the cost savings on adalimumab alone for the British National Healthcare System were £400 million (£130 million per year) [159]. Furthermore, cost savings achieved with the introduction of biosimilars in the United Kingdom improved patient care. For example, prior to 2021, patients with rheumatoid arthritis in the UK could only receive biological treatment only if they had *severe* disease that had not responded to conventional DMARDs. However, the 2021 guidelines of the National Institute of Health and Care Excellence

(NICE) extended the use TNF inhibitors for *moderate* rheumatoid arthritis unresponsive to conventional DMARDs [160,161].

In Norway, access to biologic treatments has also improved considerably following the introduction of biosimilars while costs decreased, and this allowed Norwegian rheumatologists to start treatment with biologic DMARDs earlier and at lower levels of disease activity across all inflammatory joint diseases [162]. There was an increased use of 100% for infliximab (2015 to 2021); >200% for adalimumab (2018 to 2021); 50% for etanercept (2016 to 2021) [133]. Overall, since the introduction of biosimilars, the use of TNF inhibitors in Norway has increased by 300–400% [160].

In Germany, an analysis of claims data conducted in Bavaria in 2014–2019 (when three biosimilars entered the market) on patients with inflammatory rheumatic diseases showed an increase in the proportion of targeted treatments (from 12.3% to 20.4%) and a reduction in treatment duration before first-time bDMARD (from 3.15 to 2.17 years) [163].

Furthermore, in some European countries a proportion of cost savings derived from biosimilars use is shared and reinvested in the hospital in order to improve healthcare assistance. For example, in the United Kingdom this has allowed hospitals to recruit more nurses, improve infrastructure or providing better training for non-specialist healthcare professionals [160].

However, the principle that the lower price of biosimilars leads to increased access to biological treatment is not always valid outside of the European Union, as in some jurisdictions coverage may not be conditioned by the price of the molecule. A notable example in this sense is the United States, where the use of the reference biologics remains high even for those drugs that have biosimilars available. The low biosimilar adoption rate in the United States has many causes, including patent disputes, tactics of the reference drug manufacturer to delay biosimilar market entry and, importantly, rebate agreements between pharmaceutical companies and pharmacy benefits managers (PBMs) that grant PBMs and insurers substantial rebates for using the reference biologic (biosimilars, while being more cost-effective, offer them lower financial incentives for their use) [133].

Another advantage from the introduction of biosimilars in psoriasis is that they may allow access to biological treatment to patients living in third-world countries with pharmaceutical budget constraints [164-166]. Lastly, in those countries in which the cost of biosimilars is approaching that of conventional systemic agents, the use of TNF- α inhibitors biosimilars as first-line systemic treatment for moderate-to-severe psoriasis has been proposed [167].

A limitation of this study is represented by the fact that the German center included in the survey could not provide discounted net prices, which makes the comparison with other countries distorted. Furthermore, although all centers analyzed are large university centers with large volumes of psoriatic patients treated with biologics, they may differ in factors that influence the price such as purchase volumes and payment terms, which may impact their representativeness at a country level.

CONCLUSION

In conclusion, the existence of multiple pricing mechanisms enhances price competition and provides significant financial savings to healthcare systems. There are, however, relevant differences in pricing policies and tendering practices across European countries that lead to significant price variations. Such price variability may have a remarkable impact on healthcare costs and influence psoriasis patients' access to biological treatment.

REFERENCES

1. Sewerin P, Brinks R, Schneider M, Haase I, Vordenbäumen S. Prevalence and incidence of psoriasis and psoriatic arthritis. *Ann Rheum Dis*. 2019; 78:286–7.
2. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA*. 2020;323(19):1945-1960.
3. Parisi R, Iskandar IYK, Kontopantelis E, et al. National, regional, and worldwide epidemiology of psoriasis: Systematic analysis and modelling study. *BMJ*;369:m1590.
4. Langley RGB, Krueger GG, Griffiths CEM. Psoriasis: epidemiology, clinical features, and quality of life. *Annals of the Rheumatic Diseases* 2005;64:ii18-ii23.
5. Dand N, Mahil SK, Capon F, et al. Psoriasis and genetics. *Acta Derm Venereol* 2020;100:adv00030.
6. Raharja A, Mahil SK, Barker JN. Psoriasis: a brief overview. *Clin Med (Lond)*. 2021;21(3):170-173.
7. Trembath RC, Clough RL, Rosbotham JL, Jones AB, Camp RD, Frodsham A, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet*;6:813–20.
8. Nair RP, Henseler T, Jenisch S, Stuart P, Bichakjian CK, Lenk W, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. *Hum Mol Genet*;6:1349–56.
9. Capon F, Semprini S, Dallapiccola B, Novelli G. Evidence for interaction between psoriasis-susceptibility loci on chromosomes 6p21 and 1q21. *Am J Hum Genet*;65:1798–800.
10. Enlund F, Samuelsson L, Enerback C, Inerot A, Wahlstrom J, Yhr M, et al. Analysis of three suggested psoriasis susceptibility loci in a large Swedish set of families: confirmation of linkage to chromosome 6p (HLA region), and to 17q, but not to 4q. *Hum Hered*;49:2–8.
11. Veal CD, Clough RL, Barber RC, Mason S, Tillman D, Ferry B, et al. Identification of a novel psoriasis susceptibility locus at 1p and evidence of epistasis between PSORS1 and candidate loci. *J Med Genet* 2001;38:7–13.
12. Nair RP, Stuart P, Henseler T, Jenisch S, Chia NV, Westphal E, et al. Localization of psoriasis-susceptibility locus PSORS1 to a 60-kb interval telomeric to HLA-C. *Am J Hum Genet*. 2000;66: 1833–44.

13. Capon F, Novelli G, Semprini S, Clementi M, Nudo M, Vultaggio P, et al. Searching for psoriasis susceptibility genes in Italy: genome scan and evidence for a new locus on chromosome 1. *J Invest Dermatol* 1999;112:32–5.
14. Enlund F, Samuelsson L, Enerback C, Inerot A, Wahlstrom J, Yhr M, et al. Psoriasis susceptibility locus in chromosome region 3q21 identified in patients from southwest Sweden. *Eur J Hum Genet* 1999;7:783–90.
15. Matthews D, Fry L, Powles A, Weber J, McCarthy M, Fisher E, et al. Evidence that a locus for familial psoriasis maps to chromosome 4q. *Nat Genet* 1996;14:231–3.
16. Tomfohrde J, Silverman A, Barnes R, Fernandez-Vina MA, Young M, Lory D, et al. Gene for familial psoriasis susceptibility mapped to the distal end of human chromosome 17q. *Science* 1994;264:1141–5.
17. Lee YA, Ruschendorf F, Windemuth C, Schmitt-Egenolf M, Stadelmann A, Nurnberg G, et al. Genomewide scan in german families reveals evidence for a novel psoriasis-susceptibility locus on chromosome 19p13. *Am J Hum Genet* 2000;67:1020–4.
18. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet* 2011;89:432–7.
19. Budu-Aggrey A, Brumpton B, Tyrrell J, et al. Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study. *PLoS Med* 2019;16:e1002739.
20. Schön MP, Erpenbeck L. The interleukin-23/interleukin-17 axis links adaptive and innate immunity in psoriasis. *Front Immunol* 2018;9:1323.
21. Zhou, X., Chen, Y., Cui, L. et al. Advances in the pathogenesis of psoriasis: from keratinocyte perspective. *Cell Death Dis* 2022;13:81.
22. Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. *Ann Rheum Dis* 2005;64(Suppl 2):ii65–8.
23. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210–6.
24. Augustin M, Krüger K, Radtke MA, Schwippl I, Reich K. Disease severity, quality of life and health care in plaque-type psoriasis: a multicenter cross-sectional study in Germany. *Dermatology* 2008;216:366–72.
25. Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. *Br J Dermatol* 2007;156:945–50.

26. Ahmed SS, Manchanda Y, De A, Das S, Kumar R. Topical Therapy in Psoriasis. *Indian J Dermatol*. 2023;68(4):437-445.
27. Purvis CG, Balogh EA, Heron CE, Feldman SR. Topical calcipotriol plus betamethasone dipropionate for the treatment of plaque psoriasis: a drug evaluation. *Expert Opin Pharmacother*. 2021;22(9):1107-1118.
28. Wang C, Lin A. Efficacy of topical calcineurin inhibitors in psoriasis. *J Cutan Med Surg*. 2014;18:8–14.
29. Zhang P, Wu MX. A clinical review of phototherapy for psoriasis. *Lasers Med Sci*. 2018;33(1):173-180.
30. Stern RS; PUVA Follow-Up Study. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *J Am Acad Dermatol*. 2012;66(4):553-62.
31. Marcil I, Stern RS. Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet*. 2001;358(9287):1042-5.
32. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION) *Br J Dermatol*. 2008;158(3):558–66.
33. Ho VC, Griffiths CE, Albrecht G, Vanaclocha F, León-Dorantes G, Atakan N, et al. Intermittent short courses of cyclosporin (Neoral(R)) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. The PISCES Study Group. *Br J Dermatol*. 1999;141(2):283–91.
34. Al-Janabi A, Yiu ZZN. Biologics in Psoriasis: Updated Perspectives on Long-Term Safety and Risk Management. *Psoriasis (Auckl)*. 2022;12:1-14.
35. Papp KA, Tying S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152(6):1304-12.
36. Menter A, Tying SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008;58:106-115.
37. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, Unnebrink K, Kaul M, Camez A: Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008; 158:558-566.

38. Gottlieb AB, Blauvelt A, Thaci D, Leonardi CL, Poulin Y, Drew J, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks from 2 phase 3, multicenter, randomized, doubleblinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). *J Am Acad Dermatol* 2018;79:302-314.
39. Lebwohl M, Blauvelt A, Paul C, Sofen H, Węglowska J, Piguet V, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT). *J Am Acad Dermatol* 2018;79:266-276.
40. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;366:1367-1374.
41. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007;56 31.e1-15.
42. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med* 2014;371:326-338.
43. Bagel J, Nia J, Hashim PW, et al. Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-week CLARITY results). *Dermatol Ther (Heidelb)*. 2018;8(4):571–579.
44. Papp KA, Leonardi CL, Blauvelt A, Reich K, Korman NJ, Ohtsuki M, et al. Ixekizumab treatment for psoriasis: integrated efficacy analysis of three double-blinded, controlled studies (UNCOVER-1, UNCOVER2, UNCOVER-3). *Br J Dermatol* 2018;178:674-681.
45. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol* 2016;175:273-286.
46. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med* 2015;373:1318-1328.
47. Reich K, Papp KA, Blauvelt A, Langley RG, Armstrong A, Warren RB, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind,

active comparator and placebo controlled phase 3 trial. *Lancet*. 2021;397(10273):487-498.

48. Smolen JS, Sebba A, Ruderman E, et al. Efficacy and safety of ixekizumab versus adalimumab (spirit-H2h) with and without concomitant conventional synthetic disease-modifying antirheumatic drugs (dmard) in biologic dmard-naïve patients with psoriatic arthritis: 52-week results. *Ann Rheum Dis*. 2020;79(Suppl 10):143–144.

49. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, doubleblind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371:1665-1674.

50. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371:1675-1684.

51. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405–417.

52. Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet*. 2019;394(10201):831–839.

53. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet*. 2018;392(10148):650-661.

54. Warren RB, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab vs. secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): results from a phase III, randomized, open-label, efficacy–assessor-blinded clinical trial. *Br J Dermatol*. 2020.

55. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol*. 2017;76(3):405–417.

56. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288.
57. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1). *J Am Acad Dermatol*. 2015;73(1):37-49.
58. Daudén E, de la Cueva P, Salgado-Boquete L, Llamas-Velasco M, Fonseca E, Pau-Charles I, et al. Efficacy and Safety of Dimethyl Fumarate in Patients with Moderate-to-Severe Plaque Psoriasis: Results from a 52-Week Open-Label Phase IV Clinical Trial (DIMESKIN 1). *Dermatol Ther (Heidelb)*. 2023;13(1):329-345.
59. Lebwohl M, Warren RB, Sofen H, Imafuku S, Paul C, Szepietowski JC, et al. Deucravacitinib in plaque psoriasis: 2-year safety and efficacy results from the phase III POETYK trials. *Br J Dermatol*. 2024;190(5):668-679.
60. Armstrong AW, Gooderham M, Warren RB, Papp KA, Strober B, Thaçi D, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. *J Am Acad Dermatol*. 2023;88(1):29-39.
61. Gisondi P, Bellinato F, Curic T, Girolomoni G. Biosimilars for the Treatment of Moderate to Severe Chronic Plaque Psoriasis. *Psoriasis (Auckl)*. 2025;15:401-410.
62. Reese R, Nanavath SR, Martin J, Travers JB, Rohan CA. A review of biosimilars in psoriasis: impacts on efficacy, safety, access, and a first-hand look at biosimilar cost savings within the department of veterans affairs. *J Dermatolog Treat*. 2024;35(1):2402912.
63. Jørgensen KK, Olsen IC, Goll GL, et al. NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389(10086):2304-2316. *Lancet*. 2017;389(10086):2286.
64. Griffiths CEM, Thaci D, Gerdes S, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *Br J Dermatol*. 2017;176(4):928–938.
65. Papp K, Bachelez H, Costanzo A, Foley P, Gooderham M, Kaur P, et al. Clinical similarity of the biosimilar ABP 501 compared with adalimumab after single transition:

long-term results from a randomized controlled, double-blind, 52-week, phase III trial in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2017;177(6):1562-1574.

66. Lebwohl MG, Koo JY, Jaworski J, Trefler J, Daniluk S, Dudek A, et al. Repeated Switching Between CT-P17 and EU Reference Adalimumab in Patients with Moderate-to-Severe Chronic Plaque Psoriasis: A Randomized, Double-Blind, Active-Controlled, Phase 3, Interchangeability Study. *Adv Ther*. 2025;42(3):1582-1599.

67. Feldman SR, Reznichenko N, Pulka G, Kingo K, George Galdava, Berti F, et al. Efficacy, Safety and Immunogenicity of AVT02 Versus Originator Adalimumab in Subjects with Moderate to Severe Chronic Plaque Psoriasis: A Multicentre, Double-Blind, Randomised, Parallel Group, Active Control, Phase III Study. *BioDrugs*. 2021;35(6):735-748.

68. Feldman SR, Reznichenko N, Berti F, et al. Randomized, double-blind, multicenter study to evaluate efficacy, safety, tolerability, and immunogenicity between AVT04 and the reference product ustekinumab in patients with moderate-to-severe chronic plaque psoriasis. *Expert Opin Biol Ther*. 2023;23(8):759–771.

69. Feldman SR, Narbutt J, Girolomoni G, Brzezicki J, Reznichenko N, Zegadło-Mylik MA, et al. A randomized, double-blind, phase III study assessing clinical similarity of SB17 (proposed ustekinumab biosimilar) to reference ustekinumab in subjects with moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2024;91(3):440-447.

70. Papp KA, Lebwohl MG, Thaçi D, et al. Efficacy and safety of candidate biosimilar CT-P43 versus originator ustekinumab in moderate to severe plaque psoriasis: 28-week results of a randomised, active-controlled, double-blind, phase III study. *BioDrugs*. 2024;38(1):121–131.

71. Blauvelt A, Papp K, Trivedi M, et al. Efficacy and safety of the ustekinumab biosimilar ABP 654 in patients with moderate-to-severe plaque psoriasis: a randomized double-blinded active-controlled comparative clinical study over 52 weeks. *Br J Dermatol*. 2025;192(5):826–836.

72. Morita A, Nishikawa K, Yamada F, Yamanaka K, Nakajima H, Ohtsuki M. Safety, efficacy, and drug survival of the infliximab biosimilar CT-P13 in post-marketing surveillance of Japanese patients with psoriasis. *J Dermatol*. 2022;49(10):957-969.

73. Dapavo P, Vujic I, Fierro MT, Quaglino P, Sanlorenzo M. The infliximab biosimilar in the treatment of moderate to severe plaque psoriasis. *J Am Acad Dermatol*. 2016;75(4):736-739.

74. Gisondi P, Bianchi L, Conti A, et al. Infliximab biosimilar CT-P13 in the treatment of chronic plaque psoriasis: data from the Psobiosimilars registry. *Br J Dermatol*. 2017;177(6):e325–e326.
75. Gisondi P, Virga C, Piaserico S, Meneguzzo A, Odorici G, Conti A, Girolomoni G. Switching from one infliximab biosimilar (CT-P13) to another infliximab biosimilar (SB2) in patients with chronic plaque psoriasis. *Br J Dermatol*. 2020;183(2):397-398.
76. Owczarek W, Walecka I, Nowakowska A, Ciechanowicz P, Reich A, Lesiak A, et al. Effectiveness of infliximab biosimilars in the treatment of moderate to severe chronic plaque psoriasis: experience of real-world data from the register of the program "Treatment of moderate and severe forms of plaque psoriasis (B.47)" of the National Health Fund in Poland. *Postepy Dermatol Alergol*. 2022;39(4):723-728.
77. Giordano D, Capalbo A, Gagliostro N, et al. Biosimilar versus originator etanercept: a real-life clinical study. *Ital J Dermatol Venerol*. 2022;157(4):318–324.
78. Gisondi P, Bianchi L, Calzavara-Pinton P, et al. Etanercept biosimilar SB4 in the treatment of chronic plaque psoriasis: data from the psobiosimilars registry. *Br J Dermatol*. 2019;180(2):409–410.
79. Egeberg A, Ottosen MB, Gniadecki R, Broesby-Olsen S, Dam TN, Bryld LE, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2018;178(2):509-519.
80. Phan DB, Jourdain H, Descalzo-Gallego MA, et al. Drug survival and safety of biosimilars for treating psoriasis compared with originator Adalimumab: a multinational cohort study. *Br J Dermatol*. 2025;192(4):641–652.
81. Phan DB, Bewley AP, Laws P, Mackenzie T, Smith CH, Griffiths CEM et al. Effectiveness of Adalimumab Biosimilars and Originator for Psoriasis. *JAMA Dermatol*. 2025;161(4):358-366.
82. Loft N, Egeberg A, Rasmussen MK, Bryld LE, Nissen CV, Dam TN, Ajeiy KK, et al. Outcomes Following a Mandatory Nonmedical Switch From Adalimumab Originator to Adalimumab Biosimilars in Patients With Psoriasis. *JAMA Dermatol*. 2021;157(6):676-683.
83. Egeberg A, Girolomoni G, Feldman SR, Radtke MA, Carrascosa JM, Ghil J, et al. Real World SB4 (Etanercept Biosimilar) Use in Patients With Psoriasis: Data from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *J Drugs Dermatol*. 2020;19(3):316-318.
84. Girolomoni G, Feldman SR, Egeberg A, Puig L, Jung J, Jung H, et al. Long-term real-world evidence of SB5 (adalimumab biosimilar) treatment in patients with moderate-to-

severe psoriasis from the British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR). *J Dermatolog Treat.* 2024;35(1):2434091.

85. Takeuchi T, Nishikawa K, Yamada F, Morita A, Ohtsuki M, Suzuki Y, et al. Real-World Safety and Efficacy of Biosimilar CT-P13 in Patients with Immune-Mediated Inflammatory Diseases: Integrated Analysis of Three Japanese Prospective Observational Studies. *Drug Saf.* 2023;46(10):991-1005.

86. Shams K, Salvati C, Bachinskaya E, Foierl T. Safety outcomes with GP2015 (etanercept biosimilar) in psoriasis: real-world evidence from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). *Br J Dermatol.* 2025;193.

87. Papp K, Bachelez H, Costanzo A, Foley P, Gooderham M, Kaur P, et al. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *J Am Acad Dermatol.* 2017;76(6):1093-1102.

88. Menter A, Cohen S, Kay J, Strand V, Gottlieb A, Hanauer S, et al. Switching Between Adalimumab Reference Product and BI 695501 in Patients with Chronic Plaque Psoriasis (VOLTAIRE-X): A Randomized Controlled Trial. *Am J Clin Dermatol.* 2022;23(5):719-728.

89. IQVIA. The Impact of Biosimilar Competition in Europe 2024. Available from: <https://www.iqvia.com/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2024>.

90. EMA. Biosimilar medicines: Overview. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview>.

91. Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU. Available from: https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf

92. The French Biosimilars Market. Available from: <https://smart-pharma.com/wp-content/uploads/2024/06/The-French-Biosimilars-Market-2027-Perspectives-VF.pdf>

93. Moorkens E, Barcina Lacosta T, Vulto AG, Schulz M, Gradl G, Enners S, et al. Learnings from Regional Market Dynamics of Originator and Biosimilar Infliximab and Etanercept in Germany. *Pharmaceuticals (Basel).* 2020;13(10):324.

94. Barcina Lacosta T, Vulto AG, Huys I, Simoens S. An exploration of biosimilar TNF-alpha inhibitors uptake determinants in hospital environments in Italy, Portugal, and Spain. *Front Med (Lausanne)*. 2023;9:1029040.
95. Esplugues FJ, Andújar I, Esplugues JV. The impact of EU public procurement regulations on tenders in Spain: a study with adalimumab. *Front Pharmacol*. 2024;15:1447324.
96. Commissioning framework for best value biological medicines. Available from: <https://www.england.nhs.uk/long-read/commissioning-framework-for-best-value-biological-medicines/>
97. Lee MK, Della Loggia L, Yadav V, Straccia V. Assessing the Impact of Access Policies on Biosimilar Pricing: A Comparative Study of Five Major European Markets. *Value in Health* 2024;27(12):S2.
98. Price negotiations and tendering. From <https://amgros.dk/pharmaceuticals/price-negotiations-and-tendering/>
99. Mestre-Ferrandiz J, Czech M, Smolen JS, Cornes P, Aapro MS, Danese S, et al. Capturing the holistic value of biosimilars in Europe - part 1: a historical perspective. *Expert Rev Pharmacoecon Outcomes Res*. 2024;24(2):237-250.
100. Böhm AK, Steiner IM, Stargardt T. Market diffusion of biosimilars in off-patent biologic drug markets across Europe. *Health Policy*. 2023;132:104818.
101. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, et al. Psoriasis and comorbid diseases: Epidemiology. *J Am Acad Dermatol*. 2017;76(3):377-390.
102. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006;54(8):2665-73.
103. Gisondi P, Bellinato F, Girolomoni G, Albanesi C. Pathogenesis of Chronic Plaque Psoriasis and Its Intersection With Cardio-Metabolic Comorbidities. *Front Pharmacol*. 2020;11:117.
104. Daugaard C, Iversen L, Hjuler KF. Comorbidity in Adult Psoriasis: Considerations for the Clinician. *Psoriasis (Auckl)*. 2022;12:139-150.
105. Fleming P, Bai JW, Pratt M, et al. The prevalence of anxiety in patients with psoriasis: a systematic review of observational studies and clinical trials. *J Eur Acad Dermatol Venereol* 2017;31(5):798-807.

106. Dowlatshahi EA, Wakkee M, Arends LR, et al. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *J Invest Dermatol*. 2014;134(6):1542-1551.
107. Luna PC, Chu CY, Fatani M, et al. Psychosocial Burden of Psoriasis: A Systematic Literature Review of Depression Among Patients with Psoriasis. *Dermatol Ther (Heidelb)* 2023;13(12):3043-3055.
108. Burgos-Pol R, Martínez-Sesmero JM, Ventura-Cerdá JM, Elías I, Caloto MT, Casado MÁ. The Cost of Psoriasis and Psoriatic Arthritis in 5 European Countries: A Systematic Review. *Actas Dermosifiliogr*. 2016;107(7):577-90.
109. OECD. Inflation (CPI). Available from: <https://www.oecd.org/en/data/indicators/inflation-cpi.html>
110. Finzi AF, Mantovani LG, Belisari A; Italian Association for Studies on Psoriasis. The cost of hospital-related care of patients with psoriasis in Italy based on the AISP study. *Associazione Italiana Studi Psoriasi. J Eur Acad Dermatol Venereol*. 2001;15(4):320-4.
111. Colombo G, Altomare G, Peris K, Martini P, Quarta G, Congedo M, et al. Moderate and severe plaque psoriasis: cost-of-illness study in Italy. *Ther Clin Risk Manag*. 2008;4(2):559-68.
112. Le Moigne M, Sommet A, Lapeyre-Mestre M, Bourrel R, Molinier L, Paul C, et al. Healthcare cost impact of biological drugs compared with traditional systemic treatments in psoriasis: a cohort analysis in the French insurance database. *J Eur Acad Dermatol Venereol*. 2014;28(9):1235-44.
113. Carrascosa JM, Pujol R, Daudén E, Hernanz-Hermosa JM, Bordas X, Smandia JA, Ferrándiz C. A prospective evaluation of the cost of psoriasis in Spain (EPIDERMA project: phase II). *J Eur Acad Dermatol Venereol*. 2006;20(7):840-5.
114. Sanchez-Carazo JL, Daudén E, Vanaclocha F, Toribio J, Pujol R, Puig L, et al. Cost of moderate to severe psoriasis patients in Spain. *Value Health* 2009;12:A454.
115. Berger K, Ehlken B, Kugland B, Augustin M. Cost-of-illness in patients with moderate and severe chronic psoriasis vulgaris in Germany. *J Dtsch Dermatol Ges*. 2005;3(7):511-8.
116. Schöffski O, Augustin M, Prinz J, Rauner K, Schubert E, Sohn S, Reich K. Costs and quality of life in patients with moderate to severe plaque-type psoriasis in Germany: a multi-center study. *J Dtsch Dermatol Ges*. 2007;5(3):209-18.
117. Steinke SI, Peitsch WK, Ludwig A, Goebeler M. Cost-of-illness in psoriasis: comparing inpatient and outpatient therapy. *PLoS One*. 2013;8(10):e78152.

118. Fonia A, Jackson K, Lereun C, Grant DM, Barker JN, Smith CH. A retrospective cohort study of the impact of biologic therapy initiation on medical resource use and costs in patients with moderate to severe psoriasis. *Br J Dermatol*. 2010;163(4):807-16.
119. Fowler JF, Duh MS, Rovba L, Buteau S, Pinheiro L, Lobo F, et al. The impact of psoriasis on health care costs and patient work loss. *J Am Acad Dermatol*. 2008;59(5):772-80.
120. Yu AP, Tang J, Xie J, Wu EQ, Gupta SR, Bao Y, et al. Economic burden of psoriasis compared to the general population and stratified by disease severity. *Curr Med Res Opin*. 2009;25(10):2429-38.
121. Gunnarsson C, Chen J, Rizzo JA, Ladapo JA, Naim A, Lofland JH. The direct healthcare insurer and out-of-pocket expenditures of psoriasis: evidence from a United States national survey. *J Dermatolog Treat*. 2012;23(4):240-54.
122. Feldman SR, Zhao Y, Shi L, Tran MH. Economic and Comorbidity Burden Among Patients with Moderate-to-Severe Psoriasis. *J Manag Care Spec Pharm*. 2015;21(10):874-88.
123. Al Sawah S, Foster SA, Goldblum OM, Malatestinic WN, Zhu B, Shi N, et al. Healthcare costs in psoriasis and psoriasis sub-groups over time following psoriasis diagnosis. *J Med Econ*. 2017;20(9):982-990.
124. Villacorta R, Teeple A, Lee S, Fakharzadeh S, Lucas J, McElligott S. A multinational assessment of work-related productivity loss and indirect costs from a survey of patients with psoriasis. *Br J Dermatol*. 2020;183(3):548-558.
125. Gisondi P, Bellinato F, Girolomoni G, Albanesi C. Pathogenesis of chronic plaque psoriasis and its intersection with cardio-metabolic comorbidities. *Front Pharmacol*. 2020; 11:117.
126. Wu JJ, Suryavanshi M, Davidson D, Patel V, Jain A, Seigel L. Economic Burden of Comorbidities in Patients with Psoriasis in the USA. *Dermatol Ther (Heidelb)*. 2023; 13(1):207-219.
127. Kimball AB, Guérin A, Tsaneva M, Yu AP, Wu EQ, Gupta SR, et al. Economic burden of comorbidities in patients with psoriasis is substantial. *J Eur Acad Dermatol Venereol*. 2011;25(2):157-63.
128. Feldman SR, Tian H, Gilloteau I, Mollon P, Shu M. Economic burden of comorbidities in psoriasis patients in the United States: results from a retrospective U.S. database. *BMC Health Serv Res*. 2017;17(1):337.

129. Feldman SR, Zhao Y, Shi L, Tran MH, Lu J. Economic and comorbidity burden among moderate-to-severe psoriasis patients with comorbid psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2015;67(5):708-17.
130. Cai Q, Teeple A, Wu B, Muser E. Prevalence and economic burden of comorbid anxiety and depression among patients with moderate-to-severe psoriasis. *J Med Econ*. 2019;22(12):1290-1297.
131. Pilon D, Teeple A, Zhdanava M, Ladouceur M, Ching Cheung H, Muser E, et al. The economic burden of psoriasis with high comorbidity among privately insured patients in the United States. *J Med Econ*. 2019;22(2):196-203.
132. Wu JJ, Suryavanshi M, Davidson D, Patel V, Jain A, Seigel L. Economic Burden of Comorbidities in Patients with Psoriasis in the USA. *Dermatol Ther (Heidelb)*. 2023;13(1):207-219.
133. Kvien TK, Patel K, Strand V. The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems. *Semin Arthritis Rheum*. 2022; 52:151939.
134. Ramírez-Herráiz E, Escudero-Vilaplana V, Alañón-Plaza E, Trovato-López N, Herranz-Alonso A, Morell-Baladrón A, et al. Efficiency of adalimumab, etanercept and infliximab in rheumatoid arthritis patients: dosing patterns and effectiveness in daily clinical practice. *Clin Exp Rheumatol*. 2013;31(4):559-65.
135. Beck M, Michel B, Rybarczyk-Vigouret MC, Sordet C, Sibilía J, Velten M. Biosimilar infliximab for the management of rheumatoid arthritis in France: what are the expected savings? *Eur J Hosp Pharm*. 2017;24(2):85-90.
136. EVERSANA. Biosimilar Pricing in Europe: A look at Infliximab. Available from: https://www.eversana.com/wp-content/uploads/dlm_uploads/2019/04/Biosimilar-Pricing-in-Europe-Web-Version-EVERSANA.pdf
137. Moorkens E, Godman B, Huys I, Hoxha I, Malaj A, Keuerleber S, et al. The Expiry of Humira® Market Exclusivity and the Entry of Adalimumab Biosimilars in Europe: An Overview of Pricing and National Policy Measures. *Front Pharmacol*. 2021;11:591134.
138. Determina AIFA 986/2016. *Gazzetta Ufficiale* 184 dell'8 agosto 2016. Available from: https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2016-08-08&atto.codiceRedazionale=16A05592&elenco30giorni=false
139. Determina AIFA 172/2007. *Gazzetta Ufficiale* 279 del 30 novembre 2007. Available from:

[https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2007-11-](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2007-11-30&atto.codiceRedazionale=07A09936&elenco30giorni=false)

[30&atto.codiceRedazionale=07A09936&elenco30giorni=false](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2007-11-30&atto.codiceRedazionale=07A09936&elenco30giorni=false)

140. Determina AIFA 823/2014. Gazzetta Ufficiale 190 dell'8 agosto 2014. Available from: <https://www.gazzettaufficiale.it/eli/id/2014/08/18/14A06444/sg>

141. Determina AIFA 500/2023. Gazzetta Ufficiale 173 del 26 luglio 2023. Available from:

[https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2023-07-](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2023-07-26&atto.codiceRedazionale=23A04185&elenco30giorni=false)

[26&atto.codiceRedazionale=23A04185&elenco30giorni=false](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2023-07-26&atto.codiceRedazionale=23A04185&elenco30giorni=false)

142. Determina AIFA 119/2020. Gazzetta Ufficiale 27 del 3 febbraio 2020. Available from: <https://www.gazzettaufficiale.it/eli/id/2020/02/03/20A00685/sg>

143. Determina AIFA 376/2022. Gazzetta Ufficiale 125 del 30 maggio 2022. Available from:

[https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-05-](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-05-30&atto.codiceRedazionale=22A03162&elenco30giorni=true)

[30&atto.codiceRedazionale=22A03162&elenco30giorni=true](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-05-30&atto.codiceRedazionale=22A03162&elenco30giorni=true)

144. Determina AIFA 412/2018. Gazzetta Ufficiale 79 del 5 aprile 2018. Available from: [https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2018-04-](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2018-04-05&atto.codiceRedazionale=18A02266&elenco30giorni=true)

[05&atto.codiceRedazionale=18A02266&elenco30giorni=true](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2018-04-05&atto.codiceRedazionale=18A02266&elenco30giorni=true)

145. Determina AIFA 378/2022. Gazzetta Ufficiale 125 del 30 maggio 2022. Available from:

[https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-05-](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-05-30&atto.codiceRedazionale=22A03164&elenco30giorni=true)

[30&atto.codiceRedazionale=22A03164&elenco30giorni=true](https://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2022-05-30&atto.codiceRedazionale=22A03164&elenco30giorni=true)

146. Moorkens E, Vulto AG, Huys I, et al. Policies for biosimilar uptake in Europe: an overview. PLoS One. 2017; 12(12):e0190147.

147. Barbier L, Simoens S, Soontjens C, Claus B, Vulto AG, Huys I. Off-patent biologicals and biosimilars tendering in Europe-a proposal towards more sustainable practices. Pharmaceuticals (Basel). 2021; 14(6):499.

148. Gisondi P, Geat D, Armeni P, Bellinato F, Maurelli M, Girolomoni G. Cost per responder of Adalimumab biosimilars MSB11022 and ABP 501 versus the originator and methotrexate in chronic plaque psoriasis. Expert Opin Biol Ther. 2022; 22(12):1579-1584.

149. Maurelli M, Girolomoni G, Gisondi P. Cost per responder of adalimumab biosimilars versus methotrexate in patients with psoriasis: a real-life experience. *J Dermatolog Treat.* 2023; 34(1):2218504.
150. Agenzia Italiana del Farmaco (AIFA). Elenchi farmaci di classe A e H. Available at: <https://www.aifa.gov.it/liste-farmaci-a-h>.
151. Burgos-Pol R, Martínez-Sesmero JM, Ventura-Cerdá JM, Elías I, Caloto MT, Casado MÁ. The cost of psoriasis and psoriatic arthritis in 5 European countries: a systematic review. *Actas Dermosifiliogr.* 2016; 107(7):577-90.
152. Nast A, Mrowietz U, Kragballe K, et al. Barriers to the prescription of systemic therapies for moderate-to-severe psoriasis—a multinational cross-sectional study. *Arch Dermatol Res.* 2013; 305:899–907.
153. Jha A, Upton A, Dunlop WC, Akehurst R. The budget impact of biosimilar infliximab (Remsima®) for the treatment of autoimmune diseases in five European countries. *Adv Ther.* 2015; 32(8):742-56.
154. Aladul MI, Fitzpatrick RW, Chapman SR. Impact of infliximab and etanercept biosimilars on biological disease-modifying antirheumatic drugs utilisation and NHS budget in the UK. *BioDrugs.* 2017; 31(6):533–544.
155. Aladul MI, Fitzpatrick RW, Chapman SR. The effect of new biosimilars in rheumatology and gastroenterology specialities on UK healthcare budgets: Results of a budget impact analysis. *Res Social Adm Pharm.* 2019; 15(3):310-317.
156. Barker J, Baker H, Nadeem A, Gu DH, Girolomoni G. Health economic assessment of optimal biological treatment for moderate-to-severe psoriasis. *Clin Drug Investig.* 2021; 41(11):1011-1020.
157. García-Goñi M, Río-Álvarez I, Carcedo D, Villacampa A. Budget impact analysis of biosimilar products in Spain in the period 2009-2019. *Pharmaceuticals (Basel).* 2021; 14(4):348.
158. Rognoni C, Bertolani A, Jommi C. Budget impact analysis of rituximab biosimilar in Italy from the hospital and payer perspectives. *Glob Reg Health Technol Asse.* 2018; 20:1–11.
159. Russell MD, Galloway JB. Driving down the cost of biologics: lessons from a nationalised health-care system. *Lancet.* 2024;404(10464):1723-1724.
160. Kvien TK, Betteridge N, Brückmann I, Bodenmüller W, Bryn G, Danese S, et al. Beyond Cost: Observations on Clinical and Patient Benefits of Biosimilars in Real-World Settings. *BioDrugs.* 2025;39(4):537-553.

161. National Institute for Health and Care Excellence. NICE recommends several treatment options to help with rheumatoid arthritis. 2021. Available from: <https://www.nice.org.uk/news/article/nice-recommends-several-treatment-options-to-help-with-rheumatoid-arthritis>.
162. Aga AB, Lie E, Uhlig T, Olsen IC, Wierød A, Kalstad Set al. Time trends in disease activity, response and remission rates in rheumatoid arthritis during the past decade: results from the NOR-DMARD study 2000-2010. *Ann Rheum Dis*. 2015;74(2):381-8.
163. Hörbrand F, Schuch F, Bless HH, Messinger D, Bretthauer B, Killian P. PHARAO study: drug treatment of inflammatory rheumatic diseases: guideline-conform treatment with biologics follows availability of biosimilars. *Z Rheumatol*. 2023;82:787–97.
164. Dutta B, Huys I, Vulto AG, et al. Identifying key benefits in European off-patent biologics and biosimilar markets: it is not only about price! *BioDrugs*. 2020; 34(2):159–170.
165. Inotai A, Csanadi M, Petrova G, et al. Patient access, unmet medical need, expected benefits, and concerns related to the utilisation of biosimilars in Eastern European countries: a survey of experts. *Biomed Res Int*. 2018; 2018:9597362.
166. Khraishi M, Stead D, Lukas M, et al. Biosimilars: A multidisciplinary perspective. *Clin Ther*. 2016; 38(5):1238–1249.
167. Gisondi P, Geat D, Conti A, et al. TNF- α inhibitors biosimilars as first line systemic treatment for moderate-to-severe chronic plaque psoriasis. *Expert Rev Clin Immunol*. 2020; 16(6):591-598.

SUPPLEMENTARY FILES

Supplementary Table 1. Drug costs per package of adalimumab originator and its biosimilars in Germany (in Euro).

Art	Hersteller	Anzahl pro Packung	Preis pro Packung	Preis pro Dosis
20 mg Fertigspritze	Abacus Medicine	2	520.99 €	260.50 €
	Abbvie	2	521.85 €	260.93 €
40 mg Fertigspritze	CareFarm	2	976.76 €	488.38 €
		6	2.835.94 €	472.66 €
	Abacus Medicine	1	491.72 €	491.72 €
		2	976.67 €	488.34 €
		4	2.081.54 €	520.39 €
		6	2.739.43 €	456.57 €
	A.C.A. Müller ADAG Pharma	2	977.09 €	488.55 €
		6	2.836.09 €	472.68 €
	Canoma Pharma	2	988.59 €	494.30 €
		6	2.857.12 €	476.19 €
	Eurim-Pharm Arzneimittel	2	989.02 €	494.51 €
		4	2.089.44 €	522.36 €
		6	2.858.14 €	476.36 €
	NMG Pharma	2	984.81 €	492.41 €
		6	2.739.45 €	456.58 €
	Celltrion Healthcare	2	950.23 €	475.12 €
		6	2.800.22 €	466.70 €
40 mg Fertigpen	Carefarm	2	954.55 €	477.28 €
		6	2.802.84 €	467.14 €
	Axicorp	2	952.54 €	476.27 €
		6	2.802.32 €	467.05 €
	Carefarm	2	975.30 €	487.65 €
		6	2.835.15 €	472.53 €
	Abacus	1	491.72 €	491.72 €
		2	974.46 €	487.23 €
		4	2.083.19 €	520.80 €
		6	2.833.31 €	472.22 €
	Müller Adag Pharma	2	986.07 €	493.04 €
		6	2.835.29 €	472.55 €
	Axicorp	2	974.61 €	487.31 €
		4	2.083.20 €	520.80 €
		6	2.850.86 €	475.14 €
	Emra-Med Arzneimittel	2	983.38 €	491.69 €
		4	2.083.26 €	520.82 €
		6	2.842.53 €	473.76 €
	Haemato Pharma	2	990.04 €	495.02 €
		6	2.859.17 €	476.53 €
	Medicopharm	6	2.833.17 €	472.20 €
	kohlpharma	2	989.03 €	494.52 €
		4	2.089.44 €	522.36 €
		6	2.858.17 €	476.36 €
	Oripharm	2	979.87 €	489.94 €
		4	2.084.04 €	521.01 €
		6	2.842.04 €	473.67 €
	BB Pharma	6	2.695.00 €	449.17 €
	Abacus Medicine	2	916.93 €	458.47 €
		6	2.710.01 €	451.67 €
	A.C.A. Müller ADAG Pharma	2	917.36 €	458.68 €
		6	2.716.16 €	452.69 €
	CC Pharma	2	917.28 €	458.64 €
		6	2.716.17 €	452.70 €
	NMG Pharma	6	2.797.06 €	466.18 €
80 mg Fertigpen	Abacus	1	985.63 €	985.63 €
		3	2.851.78 €	950.59 €

Supplementary Table 2. Drug costs per package of etanercept originator and its biosimilars in Germany (in Euro).

Art	Hersteller	Anzahl pro Packung	Preis pro Packung	Preis pro Dosis
25 mg Fertigspritze	Pfizer	4	690.99 €	172.75 €
		8	990.04 €	123.76 €
		24	2.859.17 €	119.13 €
50 mg Fertigpen	axicorp Pharma	4	974.94 €	243.74 €
		12	2.816.17 €	234.68 €
	European Pharma	4	873.06 €	218.27 €
		12	2.540.20 €	211.68 €
	HAEMATO PHARM	4	975.09 €	243.77 €
		12	2859.17	238.26 €
	Medicopharm	4	990.03 €	247.51 €
		12	2.847.28 €	237.27 €
	CC Pharma	4	942.84 €	235.71 €
		12	2.757.84 €	229.82 €
	Eurim-Pharm	4	968.66 €	242.17 €
		12	2.789.32 €	232.44 €
	kohlpharma	4	968.66 €	242.17 €
		12	2.789.34 €	232.45 €
50 mg Fertigspritze	Adequapharm	4	1.130.06 €	282.52 €
		12	3.335.01 €	277.92 €
	axicorp Pharma	4	974.94 €	243.74 €
		12	2.816.05 €	234.67 €
	CC Pharma	4	988.58 €	247.15 €
		12	2.852.22 €	237.69 €

Supplementary Table 3. Drug costs per package of infliximab originator and its biosimilars in Germany (in Euro).

Art	Hersteller	Anzahl pro Packung	Preis pro Packung	Preis pro Dosis
120 mg Fertigpen	Celltrion Healthcare	1	716.45 €	716.45 €
		2	1.421.62 €	710.81 €
		4	2.792.16 €	698.04 €
		6	4.118.41 €	686.40 €

Supplementary Table 4. Drug costs per package of adalimumab originator and its biosimilars in Spain (in Euro).

	AMGEVITA	HULIO	HUMIRA	HYRIMOZ	IDACIO	IMRALDI
ADALIMUMAB 40MG	54.11	-	156.75	54	42	50.00

Supplementary Table 5. Drug costs per package of etanercept originator and its biosimilars in Spain (in Euro).

	BENEPALI	ENBREL	ERELZI
ETANERCEPT 50MG	48	169.07	63

Supplementary Table 6. Drug costs per package of infliximab originator and its biosimilars in Spain (in Euro).

	FLIXABI	INFLECTRA	REMICADE	REMSIMA	ZESSLY
INFLIXIMAB 100MG	58	-	234.63	55	47.9

Supplementary Table 7. Drug costs per package of adalimumab originator and its biosimilars in Denmark (in Euro).

	Country	AMGEVITA®	HULIO®	HUMIRA®	HYRIMOZ®	IDACIO®	IMRALDI®
List price	Denmark (Aarhus)	410,87 €	Not available	633,56 €	421,40 €	Not available	405,87

Supplementary Table 8. Drug costs per package of adalimumab originator and its biosimilars in France (in Euro).

	Country	AMGEVITA®	HULIO®	HUMIRA®	HYRIMOZ®	IDACIO®	IMRALDI®
List price	France (Toulouse)	469	469	557	469	469	469
Discounted price		(2 x 40 mg syringe)	(2 x40 mg syringe)	(2 x40 mg syringe)	(2 x40 mg syringe)	(2 x40 mg syringe)	(2 x40 mg syringe)

Supplementary Table 9. Drug costs per package of etanercept originator and its biosimilars in France (in Euro).

	Country	BENEPALI®	ENBREL®	ERELZI®
List price	France (Toulouse)	524	535	524
Discounted price		(4x50 mg syringes or pen)	(4x50 mg syringes or pen)	(4x50 mg syringes or pen)

Supplementary Table 10. Drug costs per package of infliximab originator and its biosimilars in France (in Euro).

	Country	FLIXABI®	INFLECTRA®	REMICADE®	REMSIMA®	ZESSLY®
List price	France (Toulouse)	132	132	132	241 euros	NA
Discounted price		100 mg vial	100 mg vial	100 mg vial	120 mg syringe	NA

NA: not available

Supplementary Table 11. Drug costs per package of adalimumab originator and its biosimilars in Italy (in Euro).

	Country	AMGEVITA®	HULIO®	HUMIRA®	HYRIMOZ®	IDACIO®	IMRALDI®
List price	Italy (Verona)	854,84	758,68	1.068,56	758,68	758,68	758,68
Discounted price		83,16	Not applicable	286,00	47,52	47,19	49,65

Supplementary Table 12. Drug costs per package of etanercept originator and its biosimilars in Italy (in Euro).

	Country	BENEPALI®	ENBREL®	ERELZI®
List price	Italy (Verona)	696,95	1.020,52	663,34
Discounted price		Not applicable	157,08	46,75

Supplementary Table 13. Drug costs per package of infliximab originator and its biosimilars in Italy (in Euro).

	Country	FLIXABI®	INFLECTRA®	REMICADE®	REMSIMA®	ZESSLY®
List price	Italy (Verona)	428,01	428,01	513,61	428,01	428,01
Discounted price		Not applicable	129,80	288,89	71,48	56,10

RINGRAZIAMENTI

Un ringraziamento speciale al Prof. Gisondi per la sua grande disponibilità, gentilezza ed entusiasmo che mi ha accompagnato in tutto il mio percorso dagli anni della Specializzazione.

Un sentito ringraziamento, inoltre, ai Professori Luis Puig, Carle Paul, Diamant Thaçi e Lars Iversen per avere fornito i dati che sono stati utilizzati per questa tesi.