Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Wynzora 50 micrograms/g + 0.5 mg/g cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of Wynzora Cream contains 50 micrograms of calcipotriol and betamethasone dipropionate equivalent to 0.5 mg betamethasone.

Excipients with known effect:
Butylated hydroxyanisole (E 320) 1.0 mg/g cream
Macrogolglycerol hydroxystearate 3.4 mg/g cream

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cream

A white cream.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Wynzora is indicated for topical treatment of mild to moderate psoriasis vulgaris, including scalp psoriasis, in adults.

4.2 Posology and method of administration

Posology

Wynzora Cream should be applied to affected areas once daily.. Rub in the cream thoroughly in a thin layer. The recommended treatment period is up to 8 weeks. Treatment should be discontinued when control is achieved. If it is necessary to continue or restart treatment after this period, treatment should be continued only after medical review and under regular medical supervision.

When using calcipotriol containing medicinal products, the maximum daily dose should not exceed 15 g. The body surface area treated with calcipotriol containing medicinal products should not exceed 30% (see section 4.4).

If used on the scalp
All the affected scalp areas may be treated with Wynzora Cream.

Special populations

Renal and hepatic impairment
The safety and efficacy of Wynzora Cream in patients with severe renal insufficiency or severe hepatic disorders have not been evaluated.

Paediatric population
The safety and efficacy of Wynzora Cream in children below 18 years have not been established.
Currently available data in children aged 12 to 17 years are described in sections 4.8, 5.1 and 5.2.

Method of administration

Wynzora Cream should not be applied directly to the face or eyes. In order to achieve optimal effect, it is not recommended to take a shower or bath, immediately after application of Wynzora Cream.. It is recommended to allow 8 hours between the application and showering to avoid washing it off.

Hands must be washed after use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Wynzora Cream is contraindicated in erythrodermic, exfoliative and pustular psoriasis.

Due to the content of calcipotriol, Wynzora Cream is contraindicated in patients with known disorders of calcium metabolism (see section 4.4).

Due to the content of corticosteroid, Wynzora Cream is contraindicated in the following conditions: Viral (e.g. herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to tuberculosis, perioral dermatitis, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers and wounds (see section 4.4).

4.4 Special warnings and precautions for use

Effects on endocrine system

Adverse reactions found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic control of diabetes mellitus may occur also during topical corticosteroid treatment due to systemic absorption.

Application under occlusive dressings should be avoided since it increases the systemic absorption of corticosteroids. Application on large areas of damaged skin or on mucous membranes or in skin folds should be avoided since it increases the systemic absorption of corticosteroids (see section 4.8).

HPA (hypothalamic–pituitary–adrenal) axis suppression was evaluated in adult subjects (N=27) with extensive psoriasis (including scalp). Adrenal suppression was seen in 1 out of 27 subjects (3.7%) after 4 weeks of treatment, and in one additional patient after 8 weeks of treatment.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for a referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Effects on calcium metabolism

Due to the content of calcipotriol in Wynzora Cream, hypercalcaemia may occur. Serum calcium is normalised when treatment is discontinued. The risk of hypercalcaemia is minimal when the maximum daily dose of Wynzora Cream (15 g) is not exceeded (see section 4.2).

Local adverse reactions

In a vasoconstrictor trial in healthy subjects, the skin blanching response of Wynzora Cream was consistent with a moderate (class II) corticosteroid when compared with other topical corticosteroids. Concurrent treatment with other steroids on the same treatment area must be avoided.

Skin of the face and genitals are very sensitive to corticosteroids. The medicinal product should not be used in these areas.

The patient must be instructed in correct use of the medicinal product to avoid application and accidental transfer to the face, mouth and eyes. Hands must be washed after each application to avoid accidental transfer to these areas.

Concomitant skin infections

When lesions become secondarily infected, they should be treated with antimicrobiological therapy. However, if infection worsens, treatment with corticosteroids should be stopped (see section 4.3).

Discontinuation of treatment

When treating psoriasis with topical corticosteroids, there may be a risk of generalised pustular psoriasis or of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post-treatment period.

Long-term use

Long-term use of corticosteroids may increase the risk of local and systemic adverse reactions. Treatment should be discontinued in case of adverse reactions related to long-term use of corticosteroid (see section 4.8).

Unevaluated use
There is no experience with the use of Wynzora Cream in guttate psoriasis.

Concurrent treatment and UV exposure

During Wynzora Cream treatment, physicians are recommended to advise patients to limit or avoid excessive exposure to either natural or artificial sunlight. Topical calcipotriol should be used with ultra-violet radiation (UVR) only if the physician and patient consider that the potential benefits outweigh the potential risks (see section 5.3).

Wynzora Cream contains butylhydroxyanisole (E 320) and macrogolglycerol hydroxystearate

Wynzora Cream contains butylhydroxyanisole (E 320) as an excipient, which may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.
Wynzora Cream contains macrogolglycerol hydroxystearate which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Wynzora Cream.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of calcipotriol/betamethasone products in pregnant women. When administered orally in animals, studies of calcipotriol have not shown teratogenic effects, though reproductive toxicity has been shown (see section 5.3). Studies in animals with glucocorticoids have shown reproductive toxicity (see section 5.3), but a number of epidemiological studies (less than 300 pregnancy outcomes) have not revealed congenital anomalies among infants born to women treated with corticosteroids during pregnancy. The potential risk for humans is uncertain. Therefore, during pregnancy, Wynzora Cream should only be used when the potential benefit justifies the potential risk.

Breastfeeding

Betamethasone is excreted in human milk, but risk of an adverse effect on the infant seems unlikely with therapeutic doses. There are no data on the excretion of calcipotriol in human milk. Caution should be exercised when prescribing Wynzora Cream to women who breast-feed. The patient should be instructed not to use Wynzora Cream on the breast when breast-feeding.

Fertility

Studies in rats with oral doses of calcipotriol or betamethasone dipropionate demonstrated no impairment of male and female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Wynzora Cream has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The estimation of the frequency of adverse reactions is based on a pooled analysis of data from clinical studies.

All reported adverse reactions were seen at a frequency below 1%. The most frequently reported adverse reactions were "Application site reactions" including application site irritation, pain, pruritus, eczema, exfoliation, telangiectasia and folliculitis.

Adverse reactions are displayed by system organ class and frequency in Table 1 below. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. The frequency of the adverse reactions is expressed according to the following categories: uncommon (≥1/1,000 to <1/100); not known (cannot be estimated from available data).

Table 1: Adverse reactions reported for Wynzora

System Organ Class	Uncommon	Not known
Infections and infestations	Application site folliculitis	
Nervous system disorders	Insomnia	
Eye disorders		Vision, blurred*
Skin and subcutaneous tissue disorders	Pruritus Rash Urticaria	
General disorders and administration site conditions	Application site irritation Application site pain Application site pruritus Application site eczema Application site exfoliation Application site telangiectasia	

* See section 4.4

Paediatric population
In an uncontrolled clinical trial with 7 subjects aged 12 to 17 years no adverse reactions were reported. See section 5.1 for further details regarding the trial.
In this limited sample, no clinically relevant differences have been observed between the safety profiles of Wynzora cream in adult and adolescent populations.

The following adverse reactions are considered to be related to the pharmacological classes of calcipotriol and betamethasone, respectively:

Calcipotriol

Adverse reactions include application site reactions, pruritus, skin irritation, burning and stinging sensation, dry skin, erythema, rash, dermatitis, eczema, psoriasis aggravated, photosensitivity and hypersensitivity reactions including very rare cases of angioedema and facial oedema.

Systemic effects after topical use may appear very rarely causing hypercalcaemia or hypercalciuria (see section 4.4).

Betamethasone (as dipropionate)

Local reactions can occur after topical use, especially during prolonged application, including skin atrophy, telangiectasia, striae, folliculitis, hypertrichosis, perioral dermatitis, allergic contact dermatitis, depigmentation and colloid milia.

When treating psoriasis with topical corticosteroids, there may be a risk of generalised pustular psoriasis.

Systemic reactions due to topical use of corticosteroids are rare in adults, however they can be severe. Adrenocortical suppression, cataract, infections, impact on the metabolic control of diabetes mellitus and increase of intra-ocular pressure can

occur, especially after long-term treatment. Systemic reactions occur more frequently when applied under occlusion (plastic, skin folds), when applied on large areas and during long-term treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Usage above the recommended dose may cause elevated serum calcium which subsides when treatment is discontinued. The symptoms of hypercalcaemia include polyuria, constipation, muscle weakness, confusion, and coma.

Excessive prolonged use of topical corticosteroids may result in adrenocortical suppression which is usually reversible. Symptomatic treatment may be indicated.

In case of chronic toxicity the corticosteroid treatment must be discontinued gradually.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsoriatics. Other antipsoriatics for topical use, Calcipotriol, combinations. ATC code: D05AX52

Mechanism of action

Wynzora Cream combines the pharmacological effects of calcipotriol hydrate as a synthetic vitamin D3 analogue and betamethasone dipropionate as a synthetic corticosteroid.

In psoriasis, vitamin D and its analogues act mainly to inhibit keratinocyte proliferation and induce keratinocyte differentiation. The underlying antiproliferative mechanism of vitamin D in keratinocytes involves the induction of the growth inhibitory factor transforming growth factor-β and of cyclin-dependent kinase inhibitors, with subsequent growth arrest in the G1 phase of the cell cycle plus down-regulation of the two proliferation factors early growth response-1 and polo-like kinase-2.

In addition, vitamin D has an immunomodulatory effect, suppressing activation and differentiation of Th17/Th1 cells while inducing a Th2/Treg response.

In psoriasis, corticosteroids suppress the immune system, particularly pro-inflammatory cytokines and chemokines, thereby inhibiting T-cell activation. At the molecular level, corticosteroids act via the intracellular glucocorticoid receptor and the anti-inflammatory function is due to transrepression of pro-inflammatory transcription factors such as nuclear factor κB, activator protein-1, and interferon regulatory factor-3.

In combination, calcipotriol and betamethasone dipropionate promote greater anti-inflammatory and anti-proliferative effects than either component alone.

Pharmacodynamic effects

HPA axis suppression was evaluated in adult subjects (N=27) with extensive psoriasis involving 20-30% of the body surface area (including scalp) under maximal usage conditions. Treatment consisted of once daily application of Wynzora Cream to the body and scalp (75% of the subjects had scalp involvement) for up to 8 weeks. Adrenal suppression was seen in 1 out of 27 subjects (3.7%) after 4 weeks of treatment, and in one additional patient after 8 weeks of treatment (N=26).

There was no trend towards decreasing cortisol levels post-ACTH stimulation with increasing systemic concentration of B17P measured as AUC_{0-7} or C_{max} or increasing average weekly amount of Wynzora Cream used.

There were no subjects that had laboratory signs of change in calcium metabolism during the treatment with Wynzora Cream.

Paediatric population

HPA axis suppression was evaluated in 7 adolescent subjects aged 12 to 17 years with extensive psoriasis involving 10.5-16% of the body surface area (including scalp). Treatment consisted of once daily application of Wynzora Cream to the body and scalp for up to 8 weeks. The mean weekly dose up to Week 8 was 27.2 g. Adrenal suppression was not observed in any subjects (N=6) after 4 or 8 weeks of treatment (one subject had an abnormal ACTH-stimulated cortisol at baseline and discontinued the trial prematurely). There were no changes in calcium metabolism.

Clinical efficacy and safety

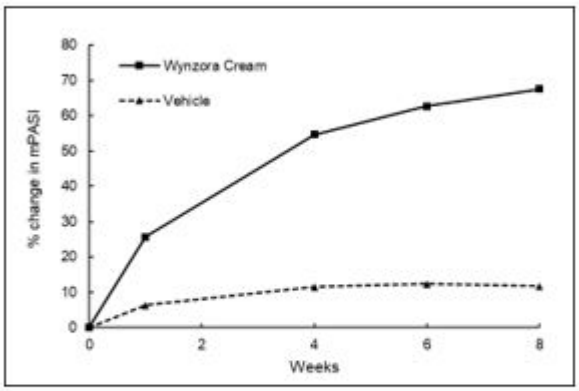
The efficacy of once daily use of Wynzora Cream was investigated in two randomised, investigator-blind, 8-week clinical trials including 738 subjects treated with Wynzora Cream or corresponding vehicle with psoriasis on the body and trunk (also scalp in trial 1) of mild to moderate severity according to the Physician's Global Assessment of disease severity (PGA). The distribution of disease severities of randomized subjects was similar in the two trials and was representative of clinical practise with the majority of subjects having mild to moderate disease, and 24% having severe disease according to BSA (more than 10% of BSA affected) and more than 12% having severe disease according to mPASI (mPASI > 12) at baseline. Wynzora Cream was effective across all disease severities. Calcipotriol/betamethasone dipropionate gel was included as an active comparator.

Results from both primary and secondary efficacy endpoints in both Trial 1 and Trial 2 demonstrated that Wynzora Cream had superior efficacy compared to vehicle ($p < 0.0001$) for all confirmatory efficacy endpoints in treating psoriasis on the body and trunk (Table 2). PGA treatment success was defined as 'clear' or 'almost clear' for patients with moderate disease at baseline and 'clear' for patients with mild disease at baseline.

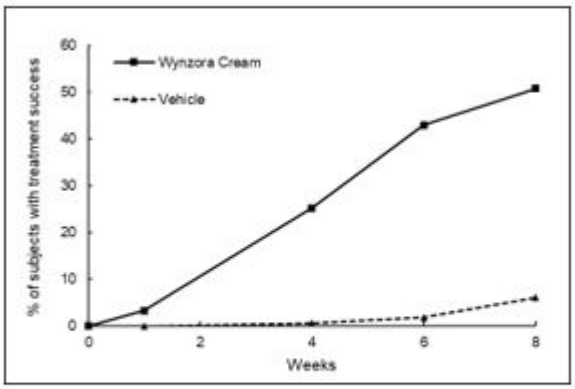
Table 2: Efficacy in Trial 1 and Trial 2 with Wynzora Cream

	Trial 1		**Trial 2**	
	Wynzora Cream N = 213	**Vehicle cream N = 68**	**Wynzora Cream N = 342**	**Vehicle cream N = 115**
Percentage of subjects with "treatment success" according to PGA at Week 8 (CI 95%)	50.7 (43.9; 57.5)	6.1 (-0.2; 12.4)	37.4 (32.1, 42.6)	3.7 (0.1, 7.2)
Mean percentage reduction in m-PASI at Week 8	67.5	11.7	62.9	22.9
PASI75 at Week 8 (CI 95%)	47.6 (40.8; 54.4)	5.1 (-0.5; 10.7)	41.6 (36.3, 47.0)	8.1 (2.8, 13.5)

Figure 1: Efficacy Results over Time in Trial 1



Trial 1: Percentage change from Baseline in mPASI. Statistically significant treatment differences towards vehicle were seen from Week 1 ($p < 0.0001$) and onwards.



Trial 1: PGA treatment success. Statistically significant treatment differences towards vehicle were seen from Week 4 and onwards ($p < 0.0001$).

Wynzora Cream has demonstrated a statistically significantly greater PGA treatment success at Week 8 compared to calcipotriol/betamethasone dipropionate gel.

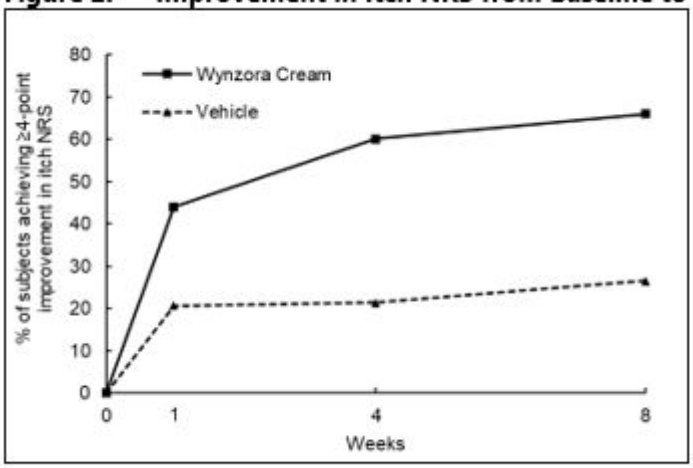
In Trial 1 the efficacy of Wynzora Cream on scalp psoriasis was investigated as the percentage of subjects with "treatment success" according to the PGA (Table 3). The efficacy of Wynzora Cream on scalp psoriasis was statistically significantly greater than vehicle at Week 4 ($p = 0.0051$) and Week 8 ($p = 0.0002$).

Table 3: Efficacy of Wynzora Cream on Scalp Psoriasis in Trial 1

	Trial 1	
	Wynzora Cream N = 112	**Vehicle cream N = 38**
Percentage of subjects with "treatment success" according to PGA at Week 8 (CI 95%)	50.8 (41.4, 60.1)	9.3 (-0.5, 19.1)

In Trial 2 Wynzora Cream demonstrated superior reduction of itch towards vehicle defined by at least a 4-point improvement in pruritus by NRS (numeric rating scale) from Baseline to Week 4. A statistically significant treatment difference ($p < 0.0001$) was seen from Week 1 and onwards.

Figure 2: Improvement in Itch NRS from Baseline to Week 4 in Trial 2 with Wynzora Cream



The effect of Wynzora Cream on quality of life was investigated in both trials. The dermatologically specific DLQI questionnaire, which relates to the degree to which the subject's skin condition affect their daily activities, showed statistically significant greater improvement in quality of life of Wynzora Cream compared to vehicle both at Week 4 ($p < 0.0001$) and Week 8 ($p < 0.0001$).

In the trials patients reported high convenience of Wynzora Cream using a validated assessment tool (Psoriasis Treatment Convenience Scale), evaluating key aspects rated by patients to be important for topical treatment, such as ease of application, lack of greasiness, moisturization and impact on daily routine.

5.2 Pharmacokinetic properties

Following systemic exposure, both active ingredients – calcipotriol and betamethasone dipropionate – are rapidly and extensively metabolised.

The main route of excretion of calcipotriol is via faeces (rats and minipigs) and for betamethasone dipropionate it is via urine (rats and mice). In rats, tissue distribution studies with radiolabelled calcipotriol and betamethasone dipropionate, respectively, showed that the kidney and liver had the highest level of radioactivity.

The extent of percutaneous absorption of the two active ingredients following topical application of Wynzora Cream was determined in the HPA axis trial in subjects with extensive psoriasis vulgaris (see section 5.1).

Plasma concentrations of calcipotriol and betamethasone dipropionate and their major metabolites were measured after 4 and 8 weeks of once daily application of Wynzora Cream.

The mean of all the analytes were within the sub-nanomolar plasma concentration range, and in most samples below or close to lower limit of quantification.

One of 27 (3.7%) adult subjects had quantifiable levels of calcipotriol at Week 4. For the major metabolite of calcipotriol, MC1080, 3 of 27 (11.1%) subjects had quantifiable levels at Week 4. No subjects had quantifiable levels of calcipotriol or MC1080 at Week 8.

For betamethasone dipropionate, there were 3 adult subjects (11.1%) with quantifiable levels of betamethasone dipropionate at Week 4. The major metabolite of betamethasone dipropionate, betamethasone 17-propionate (B17P), was quantifiable in 13 subjects (48.1%) at Week 4. No subjects had quantifiable levels of betamethasone dipropionate at Week 8, whereas 7 out of 17 (41.2%) subjects with quantifiable levels of B17P at Week 8.

Paediatric population
In a study including 7 adolescent patients (6 provided PK data), calcipotriol and its metabolite MC1080 were below the lower limit of quantification in all plasma samples at Week 4. Betamethasone dipropionate were below the lower limit of quantification in all plasma samples at Week 4. The metabolite, betamethasone 17-propionate (B17P), was quantifiable in 3 of 6 (50%) subjects.

5.3 Preclinical safety data

Studies of corticosteroids in animals have shown reproductive toxicity (cleft palate, skeletal malformations). In reproduction toxicity studies with long-term oral administration of corticosteroids to rats, prolonged gestation and prolonged and difficult labour were detected. Moreover, reduction in offspring survival, body weight and body weight gain was observed. There was no impairment of fertility. The relevance for humans is unknown.

Calcipotriol has shown maternal and foetal toxicity in rats and rabbits when given by the oral route at doses of 54 µg/kg/day and 12 µg/kg/day, respectively. The foetal abnormalities observed with concomitant maternal toxicity included signs indicative of skeletal immaturity (incomplete ossification of the pubic bones and forelimb phalanges, and enlarged fontanelles) and an increased incidence of supernumerary ribs.

The estimated systemic exposure following topical application of Wynzora Cream to psoriasis patients is negligible compared to the concentrations of calcipotriol evaluated in the oral in vivo studies, and there is no appreciable reproductive risk to humans receiving therapeutic exposure to Wynzora Cream.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

A dermal carcinogenicity study with calcipotriol in mice and an oral carcinogenicity study in rats revealed no special risk to humans.

Photo(co)carcinogenicity studies in mice suggest that calcipotriol may enhance the effect of UVR to induce skin tumours.

A dermal carcinogenicity study in mice and an oral carcinogenicity study in rats revealed no special risk of betamethasone dipropionate to humans.

In a local tolerability study in minipigs, Wynzora Cream caused mild to moderate skin irritation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isopropyl myristate
Paraffin liquid
Medium-chain triglycerides
Isopropyl alcohol
Macrogol lauryl ether
Poloxamer
Macrogolglycerol hydroxystearate
Carbomer interpolymer
Butylhydroxyanisole
Trolamine
Sodium phosphate dibasic heptahydrate
Sodium dihydrogen phosphate monohydrate
All-rac-α-tocopherol
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After first opening: 6 months.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.

6.5 Nature and contents of container

Aluminium tubes coated with epoxyphenol and with polyethylene screw cap.

Packsize: 1 tube of 60 g or multipack 120 g (1 carton containing 2 tubes of 60 g).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
Barcelona
08022
Spain

8 MARKETING AUTHORISATION NUMBER

PA0968/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th December 2021

10 DATE OF REVISION OF THE TEXT

September 2025