Agenzia Italiana del Farmaco

AIFA

Public Assessment Report

Mutual Recognition procedure

CORTIFLAM 2.250 mg medicated plaster
Bethamethasone 17-valerate

Applicant:
IBSA Farmaceutici Italia S.R.L.

Italian Marketing Authorisation Number: 035727

European procedure number: IT/H/487/001/MR

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Module 1

Information about the Initial Procedure

Product Name	CORTIFLAM
Type of application	Art 8.3(i) Dir 2001/83/EC as amended.
Active Substance	Bethamethasone 17-valerate
Form	medicated plaster 2.250 mg
Strength	2.250 mg
MA Holder	IBSA Farmaceutici Italia S.r.l. Via Martiri di Cefalonia, 2 26900 Lodi – ITALY
Reference Member State (RMS)	IT
Concerned Memember States (CMS)	FR
Procedure number	IT/H/487/001/MR
Timetable	End of procedure: Day 94 – 28 November 2016

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.
Here is reported the English version of the SMPC approved at European level.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
CORTIFLAM 2.250 mg medicated plaster.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 7.5 cm x 10 cm medicated plaster contains:
2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).

Excipients with known effect:
methyl parahydroxybenzoate (E218) (2.250 mg), (E216) propyl parahydroxybenzoate (1.125 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Medicated plaster.
Colourless plaster.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
CORTIFLAM is indicated in adults.
Treatment of inflammatory skin disorders which do not respond to treatment with less potent corticosteroids, such as eczema, lichenification, lichen planus, granuloma annulare, palmoplantar pustulosis and mycosis fungoides.
Due to its particular pharmaceutical form, CORTIFLAM is suitable for chronic plaque psoriasis localized in difficult to treat areas (e.g. knees, elbows and anterior face of the tibia on an area not greater than 5% of the body surface).

4.2 Posology and method of administration

Posology
Apply the medicated plaster to the skin area to be treated once a day. Do not exceed the maximum daily dose of six medicated plasters and the maximum treatment period of 30 days.
A new medicated plaster must be applied every 24 hours. It is also advisable to wait at least 30 minutes between one application and the next.

Once an appreciable improvement has been obtained, you can discontinue the application and possibly continue the treatment with a less potent corticosteroid.

Paediatric population

The safety and efficacy of CORTIFLAM in children aged <18 years have not yet been established.

Method of administration

Precautions to be taken before handling or administering the medicinal product

Cleanse and carefully dry the area to be treated before each application so that the medicated plaster adheres well to the skin.

Open the sachet containing the medicated plaster and cut the plaster, if necessary, so that it fits the area to be treated. Peel off the protective film and apply the adhesive medicated part to the area concerned.

Any unused part of the plaster should be put back into the sachet so that it keeps and can be used at the next application (see section 6.3).

The medicated plaster must not be removed and reused.

Once the medicated plaster has been applied, the skin must not come in contact with water. It is advisable to take a bath or have a shower between applications.

Furthermore, if the medicated plaster is applied to particularly mobile parts (e.g. an elbow or knee) and its edges start to lift, it is advisable to apply the adhesive strips for securing dressings included in the medicinal product pack.

Do not apply to face.

Never cover the medicated plaster completely with occlusive material or dressing.

4.3 Contraindications

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

Cutaneous tuberculosis and viral skin infections (including vaccinia pustules, herpes zoster and herpes simplex). Exudative lesions and primary skin infections caused by fungi or bacteria. Acne, acne rosacea, perioral dermatitis, skin ulcers, burns and frostbite.

4.4 Special warnings and precautions for use

In general, use of topical corticosteroids on large areas of the body and for prolonged periods, as well as the use of occlusive dressing can cause a temporary suppression of the hypothalamus-pituitary-adrenal axis, leading to secondary hypoadrenalism and adrenal hypercorticism, including the Cushing's syndrome. In these situations, treatment should be discontinued gradually and under strict control of a doctor due to the risk of acute adrenal insufficiency.

Sudden withdrawal of the treatment in psoriatic patients, may also lead to symptoms exacerbation or generalized pustular psoriasis.

Prolonged use of CORTIFLAM in diffuse psoriasis (except for the treatment of isolated plaques) or diffuse eczema or application on lesions located in skin folds is not recommended, as these conditions may increase systemic absorption. The use of occlusive bandages, especially with plastic material, may increase this effect. The symptoms of this are: facial redness, weight changes (fat increase in body and face and loss in legs and arms), reddish streaks on stomach, headache, menstrual alterations, or an increase in unwanted face and body hair. In this regard, it is known that certain skin areas (face, eyelids, armpits, scalp and scrotum) absorb more easily than others (skin on the knees, elbows, palms of the hands and feet on soles).

Application of topical medicinal products, especially if prolonged, may give rise to hypersensitivity reaction. Skin atrophy has also been reported after three-week treatment periods.

In case of drug intolerance, for example if skin irritation or contact dermatitis occurs during treatment, it is necessary to stop the medicated plaster application and start suitable treatment (see section 4.8 "Undesirable effects").

Corticosteroids may affect the results of the nitroblue tetrazolium test (NBT) for diagnosing bacterial infections by producing false negatives.
Medicinal products containing corticosteroids must be used with caution in patients with impaired immune system function (T-lymphocytes) or in those being treated with immunosuppressive therapy.
The product contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause hypersensitivity reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
At recommended doses, betamethasone valerate for topical use is not known to cause medically significant drug interactions. CORTIFLAM did not show significant systemic absorption of betamethasone valerate.

4.6 Fertility, pregnancy and lactation

Pregnancy
Topical administration of corticosteroids to pregnant laboratory animals may cause impairment of foetal maturation. The importance of this preclinical data has not been evaluated in humans: however, topical steroids must not be used in pregnant women on large areas of skin and specifically, in large quantities or for long period of time.
Therefore, this medicinal product must only be used in case of need and under direct medical control, after having assessed the real benefits for the mother against the possible risks for the foetus and having evaluated the treatment period and the size of the skin area to be treated.
Breast-feeding
Systemic corticosteroids are excreted in human milk.
It is unknown whether topical corticosteroids are excreted in human milk. Therefore topical corticosteroids should be used with caution also in nursing women and should not be applied to the breast.

4.7 Effects on ability to drive and use machines

CORTIFLAM has no or negligible influence on the ability to drive and use machine.

4.8 Undesirable effects

The commonly reported adverse reactions are skin and subcutaneous tissue disorders, occurring in about 15% of patients treated. These undesirable effects are mainly due to the pharmacological effects of the medicinal product. They are local effects on the skin in the plaster application area. No systemic effects have been observed.
The following list of adverse reactions has been observed during controlled clinical trials.
Reported adverse reactions have been classified according to their frequency of observation using the following convention: very common (≥1/10); common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000) and not known when cannot be estimated from the available data.
All cases reported were found to be common. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Skin and subcutaneous tissue disorders	Common	Skin atrophy Telangiectasia Pustules Papules Furuncle Erythema Pruritus Skin erosion

Other undesirable reactions not observed with CORTIFLAM, but reported with topical corticosteroids are: contact dermatitis, hypersensitivity, oedema, purpura, striae atrophicae, dry skin, skin exfoliation, capillary fragility, skin irritation, hypertrichosis, hyperaesthesia, perioral dermatitis, burning or stretching sensation, folliculitis and skin hypopigmentation.

The use of topical corticosteroids on large areas of the body and for long periods, as well as the use of occlusive dressing can cause temporary suppression of the hypothalamus-pituitary-adrenal axis, leading to secondary hypoadrenalism and adrenal hypercorticism, including the Cushing's syndrome. In these situations, treatment should be discontinued gradually and under strict control of a doctor due to the risk of acute adrenal insufficiency.

Sudden withdrawal of the treatment in psoriatic patients may also lead to symptoms exacerbation or generalized pustular psoriasis (see section 4.4 "Special warnings and precautions for use").

Hypersensitivity reactions to occlusive plastic material have been observed rarely.

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 the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

Due to the product characteristics and the route of administration, the occurrence of symptoms and signs of corticosteroid overdose is unlikely.

However, prolonged use of topical corticosteroids may cause the temporary suppression of the hypothalamus-pituitary-adrenal axis, leading to secondary hypoadrenalism. Adrenal hypercorticism symptoms spontaneously reverse and their treatment is symptomatic. If necessary, act to restore the hydroelectrolytic balance. In the event of chronic toxicity, remove the corticosteroid from the organism slowly.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids, dermatological products: active corticosteroids (group III). ATC code: D07AC01.

Betamethasone valerate for topical application is active in the treatment of dermatosis, which responds to corticosteroids, due to its anti-inflammatory, antipruriginous and vasoconstrictor action.

5.2 Pharmacokinetic properties

Absorption

Corticosteroids applied to the skin are mainly held back by the stratum corneum, and only a small part reaches the dermis where they can be absorbed. Several factors may however favour greater absorption: the location and area of the skin to be treated, the type of lesion, the treatment duration and any occlusive dressing.
In a comparative study conducted in healthy volunteers in whom 6 medicated plasters a day or an equivalent amount of cream were applied during 21 consecutive days, the levels of betamethasone (BM) measured in blood after 4 and 21 days were measurable in 11 out of 17 of the medicated plaster group and in 4 out of 10 in the cream group (LOQ= 50pg/mL). When measurable, BM blood levels in the subjects receiving the medicated plasters appeared to be slightly higher as compared to what measured in those treated with the cream. However, this difference in terms of systemic exposure had no impact on the HPA-axis function, since both the cortisol 24-h profile and the cortisol increase following ACTH stimulation test, evaluated in these same subjects, were not modified after 4 or 21 days of treatment as compared to baseline.

Metabolism

Betamethasone valerate is mainly metabolized in the liver, where it is inactivated. It is then conjugated in the liver and kidneys with sulphate or glucuronic acid.

Elimination

Betamethasone valerate is excreted in urine.

5.3 Preclinical safety data

Repeated dose toxicity have been investigated in rat after oral administration (p.o) and have shown a slight reduction in body weight gain and a reduced number of lymphocytes, eosinophils and neutrophils.
No study of reproductive toxicology has been carried out with betamethasone valerate. However, betamethasone phosphate disodium has been reported to be teratogenic in rat and rabbit with parenteral administration for systemic treatment: the most common malformation is palatoschisis that has been observed with other corticosteroids in animals.
The mutagenicity and genotoxicity of betamethasone valerate have not been observed. Skin damages, in particular epidermal and dermal thinning, were observed after repeated cutaneous corticosteroids administration in laboratory animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After opening the sachet: 1 month.

6.4 Special precautions for storage

Do not store above 25 °C.

Store the medicated plaster in its original sachet in order to preserve its integrity.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Boxes: 4 medicated plasters / 8 medicated plasters / 16 medicated plasters
Each medicated plaster is packed individually in a paper/polyethylene/aluminium/ethylene-methacrylic acid copolymer sachet.
Each box includes adhesive strips for securing dressings (medical device).
Not all pack sizes may be marketed

6.6 Special precautions for disposal

Used medicated plasters must not be flushed down toilets.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

National Information.

8. MARKETING AUTHORISATION NUMBER(S)

National Information

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

National Information
Date of first authorization: DD month YYYY
Date of latest renewal: DD month YYYY

10. DATE OF REVISION OF THE TEXT

National Information

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, the Italian version of the package leaflet for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.
Here is reported the English version of the PIL approved at European level.

Package leaflet: Information for the patient

CORTIFLAM 2.250 mg medicated plaster
Betamethasone valerate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What CORTIFLAM is and what it is used for

CORTIFLAM is a medicated plaster to be applied on the skin. It contains betamethasone valerate, which is a corticosteroid. When applied to the skin, it reduces redness, swelling and itching.
CORTIFLAM is used to treat inflamed skin conditions that do not respond to less potent corticosteroids such as eczema and psoriasis although your doctor can prescribe it for the treatment of other localized skin diseases.
CORTIFLAM is suitable for the treatment of psoriasis (patchy red skin with white scales) located in difficult to treat areas such as elbows and knees, on areas no greater than about 5 times the palm of your hand.

2. What you need to know before you use CORTIFLAM

Do not use CORTIFLAM:
- If you are allergic to betamethasone valerate or any of the other ingredients of this medicine (listed in section 6).

- If your skin disease is caused by a viral (e.g. herpes zoster, herpes simplex or vaccinia pustules), bacterial or fungal infection.
- If the skin area to be treated is affected by acne, acne rosacea, perioral dermatitis (around the mouth), skin ulcers, burns, or frostbite, or injured, with or without exuding liquid (serum).

Warning and precautions
Talk to your doctor before using CORTIFLAM.

- If you need to use it for prolonged periods and on large areas of your body, it may cause an increase in the absorption of corticosteroid into your blood. The use of occlusive bandages, especially with plastic material, may increase this effect. The symptoms of this are:
  facial redness, weight changes (fat increase in your body and face and loss in your legs and arms), reddish streaks on your stomach, headache, menstrual alterations, or an increase in unwanted face and body hair.
  In these situations, get in touch with your doctor immediately and do not interrupt the treatment without first consulting him/her.
- If you decide to discontinue the treatment. A sudden stopping of treatment in psoriasis may cause worsening of symptoms. Stopping should take place gradually and under the strict control of a doctor.
- If you are affected by widespread psoriasis or diffuse eczema or if your lesions are located in skin folds (e.g. inside of the elbow or knee, armpits, groin, genital area). In these cases, the use of CORTIFLAM for long periods is not advisable (except if treating isolated patches), since these conditions may give rise to an increase in absorption of the corticosteroid into your blood.
- CORTIFLAM acts by reducing inflammation, but if used for long periods it may irritate the skin or cause sensitization reactions. It could also damage and make skin thinner by inhibiting its natural repair process.
- If you need to do a test known as the nitroblue tetrazolium test (NBT) to check for bacterial infections, the corticosteroid contained in the medicated plaster may alter the results of this test.
- If your body is not able to cope with infections as it should, or if you are using drugs which lower your body's ability to fight off diseases (immunosuppressants). These drugs are used to prevent rejection after transplants and may also be prescribed to heal skin diseases likely to be treated with CORTIFLAM.

Children
CORTIFLAM is indicated for use in adults only.

Other medicines and CORTIFLAM
Tell your doctor if you are using, have recently used or might use any other medicines.
Since only a minimum quantity of corticosteroid is absorbed by your body, CORTIFLAM is unlikely to interact with other medicines.

CORTIFLAM with food and drink
Since only a minimum quantity of corticosteroid is absorbed by your body, CORTIFLAM is unlikely to interact with food or drink.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
CORTIFLAM may be used during pregnancy or breast-feeding only if the treatment is absolutely necessary and only upon express medical advice.

Driving and using machines
CORTIFLAM does not alter your ability to drive vehicles or use machines.

CORTIFLAM contains
Methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216). These substances may cause allergic reactions (possibly delayed).

3. How to use CORTIFLAM
Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
The recommended dose is: Apply CORTIFLAM to the skin area to be treated once a day. Do not use more than 6 medicated plasters at the same time.
A new medicated plaster must be applied every 24 hours. It is advisable to wait at least 30 minutes between one application and the next.
Do not use CORTIFLAM for more than 30 days.
Use in children and adolescents
Since no clinical data concerning use in children and adolescents is available, do not use CORTIFLAM if you are less than 18 years old.
Method of administration
Carefully clean and dry the skin area where the medicated plaster will be applied before using CORTIFLAM.
Open the sachet and cut the medicated plaster, if necessary, so that it fits the area to be treated. Peel off the protective film and apply the medicated adhesive part to the area concerned. Any unused part of the plaster should be put back into the sachet so that it can be preserved and used at the next application (see section 5).
Once removed, the medicated plaster must not be reused.
Do not get the medicated plaster wet: it is advisable to take a bath or have a shower between applications. If the edges of medicated plasters applied to particularly mobile parts (e.g. elbow or knee) lift up, apply the adhesive strips for securing dressings included in the medicinal product pack.
Do not apply to face.
Never cover the medicated plaster completely with plastic material or occlusive dressings.

If you use more CORTIFLAM than you should
Always use CORTIFLAM exactly as your doctor has told you. If you should accidentally apply more medicated plasters than your doctor prescribed on one day, do not worry, but avoid doing it again.

If you forget to use CORTIFLAM
If you forget to apply the medicated plaster for one day, apply as normal the next.
Do not apply two plasters to the same area on the same day to try to make up for the oversight.

If you stop using CORTIFLAM
If you are following the treatment correctly without seeing improvements, consult your doctor before deciding to discontinue CORTIFLAM treatment.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects which may occur when using CORTIFLAM are local effects on the skin in the plaster application area. These include: redness, itching, boils, skin eruptions with or without pus, skin thinning, the appearance of small red spots of various shapes caused by widening of the surface blood vessels and skin erosion.
Side effects which have not been observed with CORTIFLAM, but which have occurred with other topical corticosteroids include: swelling, allergic reactions, skin irritation, dry skin and skin flaking, a feeling of skin stretching, stretch marks caused by skin thinning, increase in hair growth, skin redness around the mouth and hair follicles, burning sensation and skin decolouration.
Stopping long term treatment at high doses may cause a worsening of the psoriasis including serious skin reactions with pus.
In these situations, get in touch with your doctor immediately and do not interrupt the treatment without first consulting him/her.
Long-term treatment at high doses may increase drug absorption which may lead to an increase in side effects. These effects disappear quickly and completely once the treatment is discontinued.
If your conditions get worse during treatment, you may be allergic to CORTIFLAM or require a different treatment. In this case, consult your doctor immediately.
Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CORTIFLAM
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Do not store above 25 °C.
Do not use this medicine if you notice visible sign of deterioration.
Store the medicated plaster in its original sachet in order to preserve its integrity (write the date of opening in the space provided on the inside sachet).
Once the sachet is opened, the medicated plaster must be used within 1 month.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CORTIFLAM contains:
Each 7.5 cm x 10 cm medicated plaster contains the active substance: 2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).
The other ingredients are:

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.

What CORTIFLAM looks like and contents of the pack
This medicinal product is a medicated plaster consisting of a colourless plaster. Each medicated plaster is covered with a removable protective film.
Each medicated plaster is individually packed in a sachet in boxes containing 4, 8 or 16 plasters.
Each box includes adhesive strips for securing dressings (medical device).
Not all pack sizes may be marketed

Marketing Authorisation Holder- National Information

Manufacturer
Altergon Italia S.r.l., Zona Industriale, 83040, Morra de Sanctis, Avellino (Italia)

This leaflet was last revised in
National Information

Module 4

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER LABELLING 4 medicated plasters

1. NAME OF THE MEDICINAL PRODUCT

CORTIFLAM 2.250 mg medicated plaster
Betamethasone valerate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 7.5 cm x 10 cm medicated plaster contains:
2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).

3. LIST OF EXCIPIENTS

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.
Contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. Please read the package leaflet.

4. PHARMACEUTICAL FORM AND CONTENTS

Medicated plaster
Box of 4 medicated plasters provided with adhesive strips for securing dressings

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use
Read the package leaflet before use

6 SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp: (month/year)
Once the sachet is opened, the medicated plaster must be used within 1 month.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store the medicated plaster in its original sachet in order to preserve its integrity (write the date of opening in the space provided on the inside sachet).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Used medicated plasters must not be flushed down toilets. See package leaflet inside for disposal instructions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

National Information

12. MARKETING AUTHORISATION NUMBER(S)

National Information

13. BATCH NUMBER

Batch No.:

14. GENERAL CLASSIFICATION FOR SUPPLY

National Information

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

CORTIFLAM medicated plaster

INSIDE SACHET LABELLING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CORTIFLAM 2.250 mg medicated plaster
Betamethasone valerate
Cutaneous use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 7.5 cm x 10 cm medicated plaster contains:
2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).

3. LIST OF EXCIPIENTS

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.
Contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. Please read the package leaflet.

4. METHOD OF ADMINISTRATION

Read the package leaflet before use.

5 SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out the sight and reach of children.

6. EXPIRY DATE

Exp:
Once the sachet is opened, the medicated plaster must be used within 1 month.

7. BATCH NUMBER

Batch No.:

8. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Sachet containing 1 medicated plaster.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store the medicated plaster in its original sachet in order to preserve its integrity.
Date first opened:
(to be completed by patient)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Used medicated plasters must not be flushed down toilets. See package leaflet inside for disposal instructions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

National Information

12. MARKETING AUTHORISATION NUMBER(S)

National Information

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER LABELLING 8 medicated plasters

1. NAME OF THE MEDICINAL PRODUCT

CORTIFLAM 2.250 mg medicated plaster
Betamethasone valerate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 7.5 cm x 10 cm medicated plaster contains:
2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).

3. LIST OF EXCIPIENTS

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.
Contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. Please read the package leaflet.

4. PHARMACEUTICAL FORM AND CONTENTS

Medicated plaster
Box of 8 medicated plasters provided with adhesive strips for securing dressings

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use
Read the package leaflet before use

6 SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp: (month/year)
Once the sachet is opened, the medicated plaster must be used within 1 month.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store the medicated plaster in its original sachet in order to preserve its integrity (write the date of opening in the space provided on the inside sachet).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Used medicated plasters must not be flushed down toilets. See package leaflet inside for disposal instructions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

National Information

12. MARKETING AUTHORISATION NUMBER(S)

National Information

13. BATCH NUMBER

Batch No.:

14. GENERAL CLASSIFICATION FOR SUPPLY

National Information

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

CORTIFLAM medicated plaster

INSIDE SACHET LABELLING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CORTIFLAM 2.250 mg medicated plaster
Betamethasone valerate
Cutaneous use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 7.5 cm x 10 cm medicated plaster contains:
2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).

3. LIST OF EXCIPIENTS

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.
Contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. Please read the package leaflet.

4. METHOD OF ADMINISTRATION

Read the package leaflet before use.

5 SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out the sight and reach of children.

6. EXPIRY DATE

Exp:
Once the sachet is opened, the medicated plaster must be used within 1 month.

7. BATCH NUMBER

Batch No.:

8. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Sachet containing 1 medicated plaster.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store the medicated plaster in its original sachet in order to preserve its integrity.
Date first opened:
(to be completed by patient)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Used medicated plasters must not be flushed down toilets. See package leaflet inside for disposal instructions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

National Information

12. MARKETING AUTHORISATION NUMBER(S)

National Information

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER LABELLING 16 medicated plasters

1. NAME OF THE MEDICINAL PRODUCT

CORTIFLAM 2.250 mg medicated plaster
Betamethasone valerate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 7.5 cm x 10 cm medicated plaster contains:
2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).

3. LIST OF EXCIPIENTS

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.
Contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. Please read the package leaflet.

4. PHARMACEUTICAL FORM AND CONTENTS

Medicated plaster
Box of 16 medicated plasters provided with adhesive strips for securing dressings

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Cutaneous use
Read the package leaflet before use

6 SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp: (month/year)
Once the sachet is opened, the medicated plaster must be used within 1 month.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store the medicated plaster in its original sachet in order to preserve its integrity (write the date of opening in the space provided on the inside sachet).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Used medicated plasters must not be flushed down toilets. See package leaflet inside for disposal instructions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

National Information

12. MARKETING AUTHORISATION NUMBER(S)

National Information

13. BATCH NUMBER

Batch No.:

14. GENERAL CLASSIFICATION FOR SUPPLY

National Information

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

CORTIFLAM medicated plaster

INSIDE SACHET LABELLING

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CORTIFLAM 2.250 mg medicated plaster
Betamethasone valerate
Cutaneous use

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 7.5 cm x 10 cm medicated plaster contains:
2.250 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone).

3. LIST OF EXCIPIENTS

Plaster: unwoven cloth (polypropylene/polyethylene and rayon fibres) laminated with an ethylene-methyl methacrylate copolymer film.
Adhesive layer: sodium hyaluronate, 1,3-butylene glycol, glycerol, disodium edetate, tartaric acid, aluminium glycinate, polyacrylic acid, sodium polyacrylate, hydroxypropylcellulose, carmellose sodium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), purified water.
Protective film: polyethylene terephthalate film.
Contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. Please read the package leaflet.

4. METHOD OF ADMINISTRATION

Read the package leaflet before use.

5 SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out the sight and reach of children.

6. EXPIRY DATE

Exp:
Once the sachet is opened, the medicated plaster must be used within 1 month.

7. BATCH NUMBER

Batch No.:

8. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Sachet containing 1 medicated plaster.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Store the medicated plaster in its original sachet in order to preserve its integrity.
Date first opened:
(to be completed by patient)

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Used medicated plasters must not be flushed down toilets. See package leaflet inside for disposal instructions.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

National Information

12. MARKETING AUTHORISATION NUMBER(S)

National Information

Module 5

Scientific discussion during the initial procedure

I. Introduction

Based on the review of the quality, safety, and efficacy data and the Applicant's response to the questions raised by RMS and CMS on SmPC, the RMS considers that the application for CORTIFLAM 2.250 mg medicated plaster MA No 035727; Procedure No IT/H/487/001/MR) is approvable.

The present application is a mutual recognition procedure IT/H/487/001/MR with Italy as RMS and France as CMS. The medicinal product Cortiflam 2.250 mg medicated plaster contains betamethasone valerate. Cortiflam was first authorized through National procedure in Italy on July 29, 2005 (published in the Official Italian Journal n. 189 of August 16, 2005) with legal basis: article 8(3) of DIR 2001/83/EC (full application known active substance).
The medicinal product is available in a single strength associated with one pharmaceutical form: 2.250 mg/medicated plaster.

Betamethasone valerate (BMV) was first approved for marketing in 1967 for the treatment of corticosteroid-responsive dermatoses. It is a potent glucocorticoid lacking mineralocorticoid properties and its effects are well-known both in animals and humans. BMV is of well established clinical use in the indication of severe inflammatory skin disorders.
CORTIFLAM is a transparent adhesive medicated plaster 75 cm^2-sized (75 x 100 mm) containing 2.250 mg of BMV as active ingredient (30 µg/cm^2); the concentration of the steroid in the adhesive layer is 0.1% w/w.
CORTIFLAM is indicated for cutaneous application. It has to be applied on the skin area to be treated once a day without exceeding the maximum daily dose of six medicated plasters and the maximum treatment period of 30 days.
The active substance contained in Cortiflam is betamethasone valerate. This substance is of well established use in the topical (cutaneous) treatment of severe inflammatory skin disorders, such as eczema unresponsive to less potent corticosteroids, psoriasis, lichenifications, lichen planus, granuloma annulare, palmoplantar pustulosis, mycosis fungoides, owing to its anti-inflammatory, antipruritic and vasoconstricting action.
Its safety and efficacy are confirmed by the fact that Betamethasone valerate is the active substance of many medicinal products which have already been authorised and marketed in Europe for more than 10 years such as CELESTODERM 0.1% cream (MAH: Schering Plough) and ECOVAL 0.1% cream (MAH: GLAXO SmithKline).
For the above mentioned reasons, the applicant submitted:

- references to published scientific literature in Modules 4 (Non-clinical study reports) and 5 (Clinical study reports), to demonstrate that the safety and efficacy of the active substance Betamethasone valerate are known.
- additional clinical trials, also comparing the pharmaceutical form (from a safety and efficacy point of view) to marketed medicinal products. These clinical trials were carried out in accordance with current European Guidelines: "Clinical Requirements for locally applied, locally acting products, containing known constituents" and "Clinical investigation of corticosteroids intended for use on the skin".

II. About the product

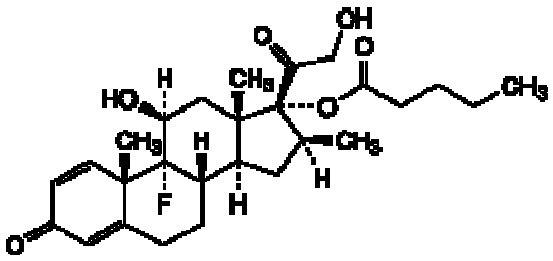
Proposed name of the medicinal product in the RMS	CORTIFLAM
Name of the drug substances (INN name):	Bethamethasone 17-valerate
Pharmaco-therapeutic group (ATC Code):	Pharmacotherapeutic group: Corticosteroids, dermatological products: active corticosteroids (group III). ATC code: D07AC01
Pharmaceutical form(s) and strength(s):	medicated plaster
Reference Number(s) for the Decentralised Procedure	**IT/H/487/001/MR**
Reference Member State:	IT
ConcernedMemberStates:	FR
Marketing Authorisation Numbers	AIC No: 035727
Name and address of the Authorization Holder	IBSA Farmaceutici Italia S.r.l. Via Martiri di Cefalonia, 2 26900 Lodi – ITALY

III. Scientific Overview and discussion

III.1 Quality aspects

International non-proprietary name (INN):	Betamethasone valerate
Systematic chemical name (IUPAC):	9-fluoro-11-hydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] pentanoate
Chemical names:	-9α-fluoro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17α-yl-valerate. -Pregna-1,4-diene-3,20-dione,9-fluoro-11β,17.21-trihydroxy-16β-methyl-valerate 9-fluoro-11β,21-dihydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl pentanoate (Ph. Eur.)
CAS registry number:	[2152-44-5]

Structural formula



Molecular formula: $C_{27}H_{37}FO_6$
Relative Molecular mass: 476.5

Chirality:
Stereochemistry:
The molecule has the absolute configuration 8S, 9R, 10S, 11S, 13S, 14S and 17R therefore isomeric forms are possible. Being the specific optical rotation a test routinely performed for the release and all batches must comply with the prescribed limits no other isomers are present.
Evaluation of IR spectrum compared with the spectrum obtained with *betamethasone 17-valerate reference substance* carried out as first identification test assures detection of any occurrence of undesired isomers.

Link to similar compounds
Structural relationship to other known drugs:
The basic chemical structure of the glucocorticoids consists of 21 carbon atoms with a total of 4 rings: three 6-carbon rings designated A, B, and C, and a five- carbon ring, D. Essential features consist of the following: 1) a 2-carbon chain at C-17; 2) methyl groups at C-18 and C-19; 3) a ketone oxygen at C-3; 4) an unsaturated bond between C-4 and C-5; 5) a hydroxyl group at C-11; and 6) a ketone oxygen at C-20.

Physical form: Solid-state form: white or almost white crystalline or microcrystalline powder; the drug substance employed in the concerned drug product is micronized;
the particle size distribution is the following:

- particles ≤ 20 µm not less than 99% of the total volume
- particles ≤ 10 µm not less than 90% of the total volume
- particles ≤ 5 µm not less than 80% of the total volume.

Solubility: Betamethasone valerate is practically insoluble in water, soluble in ethanol, freely soluble in acetone, methylene chloride and chloroform, slightly soluble in benzene and ether.

Specific optical rotation: The specific optical rotation of betamethasone valerate is +75.0 to ÷ 82.0° calculated with reference to the dried substance.

pH: Dissociation constant:

No direct measurements of the pKa of betamethasone valerate have been possible due to its aqueous insolubility.

Melting point: it melts at about 192°C with decomposition

Polymorphism: Absence of polymorphism was confirmed by DSC analysis as reported in the DMF submitted by the drug substance manufacturer to Italian Health Authorities.

The active substance is described in the relevant monograph of the European Pharmacopeia.
All aspects of the manufacture and control of the active substance Betamethasone valerate, except for the proposed packaging specifications and stability data, are covered by a Certificate of Suitability issued by EDQM.
Appropriate stability data have been generated, supporting a suitable retest period of 60 months when the drug substance is stored in the packaging proposed, double polythene liner inside a fibreboard drum.

DRUG PRODUCT

CORTIFLAM is a transparent adhesive medicated plaster 75 cm^2-sized (75 x 100 mm) containing 2.250 mg of BMV as active ingredient (30 µg/cm^2); the concentration of the steroid in the adhesive layer is 0.1% w/w.

The dosage form appears as a colourless and transparent substance, spread on unwoven cloth having characteristic odour.

Other Ingredients

Other ingredients are:

Sodium Hyaluronate, Glycerol, Disodium Edetate, Tartaric Acid, Hydroxypropylcellulose, Carmellose Sodium, Methyl Parahydroxybenzoate, Propyl Parahydroxybenzoate and Purified Water comply with the requirements of the European Pharmacopoeia, current edition.

Aluminium Glycinate complies with British Pharmacopeia.

The remaining excipients: 1,3-Butylene Glycol, Polyacrylic Acid Solution (20%), Polyacrylic Acid, Sodium Polyacrylate, Laminated unwoven cloth and Polyethylene terephthalate film comply with the respective Teikoku internal monographs.

Non-compendial excipients are tested according to specifications and test methods duly developed by the manufacturer of the medicated plaster (Teikoku Seiyaku, Japan).

These methods allow proper identification, evaluation of purity and of the relevant physical characteristics for the intended use. Reagents, test solutions and general methods follow provisions of the Japanese Pharmacopoeia.

Most of the materials used are of non-animal origin and are pharmacopoeial.

Sodium Hyaluronate is the only excipient of animal origin and it is obtained by extraction process from cock's comb.

Pharmaceutical Development

The aim of the pharmaceutical development was to formulate an innovative medicated plaster containing 0.1% of betamethasone valerate as sole drug substance.

Compared to the conventional formulations like creams and ointments, the medicated plaster shows several advantages (an occlusive dressing-technique effect, clean and fast application time, no necessity of bandage, smooth peel-off effect on the skin, protection of the treated area from scratching) and guarantees application of fixed and standardised amount of drug with reduction of number of applications/day.

Suitable pharmaceutical development data has been provided for this application.

Manufacturing Process

BV medicated plaster is formulated by mixing the drug substance (betamethasone valerate) with a plastic viscous base, mainly preformed of hydrophilic polymers (such as carmellose sodium, hydroxypropylcellulose, sodium polyacrylate, polyacrylic acid) and water, the mixed base is spread on a laminated unwoven cloth and the surface is covered with polyethylene terephthalate film (lining). BV medicated plaster is cut to an appropriate size, convenient to usage (7.5 cm x 10 cm per sheet). Basically the chosen process consists of four main phases:

Pre-mixing of solutions; Kneading; Extension and punching; Packaging and sealing.

Satisfactory batch formula has been provided for the manufacture of the medicinal product, along with an appropriate description of the manufacturing process. The manufacturing process has been validatedon three industrial batches.

Control of Finished Product
The finished product specifications are satisfactory: parameters and limits are considered adequate to control the quality of the drug product. Test methods have been described and adequately validated, as appropriate.
Batch data have been provided and comply with the release specifications.
Certificates of Analysis have been also provided.
Batch analysis data are provided for each reference standards used.

Container Closure System
The container closure system is made of paper (79.1 g/m2) / polyethylene (15 µm) / aluminium (7 µm) / ethylene methacrylic acid copolymer (20 µm) and is sealed in four directions. Segments of 7.5 x 10.0 cm are put into this package and sealed to maintain airtight condition.
The non-functional secondary packaging is a carton box containing the foreseen number of sachets and the illustrative leaflet.

Pack sizes: 4, 8 and 16 medicated plasters.

Stability
Finished product stability studies were performed according to the current ICH stability Guidelines on batches of finished product in the final proposed packaging for marketing. Based on results, a shelf life of 3 years has been justify when the drug product is properly kept in its intact packaging.
The product must be stored at a temperature not exceeding 25°C.
The product has a validity of 30 days after first opening of the sachet, if correctly stored.

III.2 Non-clinical aspects

Pharmacology

The applicant provided several publications related to the pharmacological action of BMV in animals and humans. Briefly, BMV is a synthetic fluorinated corticosteroid. Following topical application, BMV produces antiinflammatory and vasoconstrictor action. The activity of these drugs is thought to result at least in part from binding with a steroid receptor. Like other steroids, BMV decreases inflammation by stabilizing leukocyte lysosomal membranes; preventing release of destructive acid hydrolases from leukocytes; inhibiting macrophage accumulation in inflamed areas; reducing leukocyte adhesion to capillary endothelium; reducing capillary wall permeability and edema formation; decreasing complement components; antagonizing histamine activity and release of kinin from substrates; reducing fibroblast proliferation, collagen deposition and subsequent scar tissue formation, and possibly by other mechanisms as yet unknown.

Pharmacokinetics

Pharmacokinetic data indicate that following topical application of BMV on most areas of normal skin, only minimal amounts of the drug reach the dermis and subsequently the systemic circulation; however,

absorption may be increased when the skin has lost its keratin layer, as well as by inflammation and/or diseases of the epidermal barrier. Pre-clinical investigations show that about 10% of the BMV applied in vivo on canine skin penetrates the dermal layers over a 24-hour period, thus raising the systemic circulation. Extrapolation of these data to humans indicates that BMV is hardly found in the plasma at pharmacologically active concentrations after CORTIFLAM application.

Toxicology

Toxicology of betamethasone and BMV was investigated in animals; sufficient data are available to evaluate the safety profile of BMV on a bibliographic basis (acute and repeated dose toxicity, reproductive toxicity, mutagenesis and carcinogenesis). The only problems to be addressed with this formulation of BMV are local irritation, atrophogenicity and sensitisation; all these points have been addressed by clinical trials in human volunteers and patients. In addition, the poor percutaneous absorption suggests that suppression of the HPA-axis is a remote possibility after topical application and it is observed only with high doses of BMV after systemic administration.

Concerning the quality of the product, all excipients present in the formulation are known substances whose characteristics comply either with the requirements of the European Pharmacopoeia and British Pharmacopoeia (Aluminium glycinate) or with the specifications of Manufacturer's (Teikoku) internal monographs (sodium polyacrylate and 1,3-butylene glycol).

For both excipients, sufficient toxicology data exist to support their use in pharmaceutical forms for human use. As regards to the impurity profile, no safety concern should be raised, based on the data reported in the Quality Section of Applicant's Dossier.

Taking into consideration the well-known toxicity profile of betamethasone valerate (BMV), as well as of the components of the medicated plaster, and the poor systemic absorption of BMV after topical (cutaneous) application, the submitted pharmaco-toxicological references are considered sufficient to support the clinical use of CORTIFLAM for dermal application in humans.

Ecotoxicity/environmental risk assessment (ERA)

With regard to the Environmental Risk Assessment, since the crude PEC value (crude predicted concentration of the substance in surface water) is much below than 0.01 µg/L and, since no other environmental concerns are apparent, the medicinal product *Cortiflam 2.250 mg medicated plaster* is unlikely that represents a risk for the environment following its prescribed usage in patients. Anyway, the following words is included in the product patient information leaflet in order to sensitize patients to protect environment: "*Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment*." And the following words is included in the product labelling: "*Used medicated plasters must not be flushed down toilets. See package leaflet inside for disposal instructions.*"

No further actions have to be taken.

III.3 Clinical aspects

Pharmacokinetics/Pharmacodynamics

The pharmacology of Betamethasone valerate, the active ingredient of CORTIFLAM is well known.

The applicant submitted a clinical overview summarizing relevant published studies which have been included in the dossier and the results of several original clinical trials which address pharmacological aspects.

The pharmacodynamic assays in healthy volunteers and psoriatic subjects show sufficient consistency of results and allow to correctly assess the corticosteroid formulation potency. The provided clinical pharmacological data are considered sufficient and adequate in order to support the Applicant's claims for the product.

Clinical efficacy

Clinical studies results indicate that the psoriatic lesions treated with CORTIFLAM disappear or are reduced to a significantly greater extent than those treated with Celestoderm. The difference in efficacy as compared to the cream formulation is both statistically and clinically relevant (Peris 2001, 2002, 2003).

A multicentre, prospective, assessor-blind, in parallel groups randomised study confirmed the efficacy and safety of IBSA BMV medicated plaster for the treatment of chronic plaque psoriasis versus reference marked product (Naldi, 2009).

A multicentre, prospective, assessor-blind, in parallel groups randomised and controlled trial compared the efficacy and safety of BMV versus 50 µg-0,5mg/g calcipotriol - betamethasone (dipropionate) ointment (Daivobet/Dovobet), in the treatment of chronic plaque psoriasis (Ortonne, 2001)".

These three studies were evaluated and authorized for medicinal product BETESIL during the procedure IT/H/128/001/II/014.

A prospective, multicentre, opne label, observational study evalueted the efficacy of Cortiflam in psoriasis, eczema and othger dermatosisi (atopic dermatitis, contact dermatiits, lichenifications, liche planus, granuloma annulare and palmopalntar pustolosis (Maccari, 2015).

Clinical safety

The safety information contained in the proposed SmPC of CORTIFLAM seems to be in line with data emerging from clinical trials, pharmacovigilance data and literature.

No systemic adverse events were reported either with CORTIFLAM or with the reference products in the clinical trials performed by the Applicant. Neither death nor serious adverse events occurred. The adverse events recorded with CORTIFLAM were local, mild-to-moderate and transient in nature, and reflect the usual pattern of AEs for topically applied steroids: most commonly reported adverse events were papulopustules and other minor skin reactions such as pruritus, erythema, furuncules, eczema.

Important safety aspects of topical corticosteroids, such as athrophogenicity potential and HPA-axis interference, potential for irritation and sensitisation, were addressed by the Applicant by means of specific studies. Particularly, no difference was found between CORTIFLAM and marketed BMV 0.1% cream formulations taken as reference, in terms of athrophogenic effects.

Possible interference of CORTIFLAM administration on HPA-axis function was assessed by measuring morning serum cortisol in the RIPT study, in one clinical study and by means of an ad hoc safety study (exposure maximisation study): no medically significant systemic effect on HPA-axis function should be expected following the use of the product in the claimed indications, at the recommended dose (i.e max.dose = 6 plasters/day), according to the study results.

Based on the provided data, no new safety signal was identified and the incidence of the more frequents events registered in the studies – local skin reactions – remain in the range of this therapeutic class. There are no particularly important events that would need to be monitored once the product is on the market.

In conclusion, CORTIFLAM displays a comparable safety profile when compared to already approved topical formulations containing BMV and it is considered to have a positive risk/benefit ratio for the proposed indications.

Pharmacovigilance system

The MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

The Applicant has submitted an RMP version 1.1. the same as evaluated and approved for BETESIL, procedure IT/H/128/001/II/017.

SUMMARIES OF PRODUCT CHARACTERISTICS (Sm.PCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING

The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the originator products, where appropriate, along with current guidelines. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.
The packed leaflet has been evaluated via user consultation study in accordance with the requirements of articles 59(3) and 61(1) of directive 2001/83/EC. The language used for the purpose of the user testing PIL was English.

IV Overall conclusions and benefit-risk assessment

The quality characteristics of CORTIFLAM 2.250 mg medicated plaster are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.
CORTIFLAM displays a comparable safety profile when compared to already approved topical

formulations containing BMV and it is considered to have a positive risk/benefit ratio for the proposed indications.

The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFITI RISK ASSESSMENT

Based on available data the overall benefit-risk profile of the product is positive.