Stability, *in vitro* release and preliminary clinical studies of topical emulsion for cutaneous T-cell lymphoma (CTCL) containing Betamethasone Dipropionate 0.1% w/w

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Background

Cutaneous Lymphoma are an heterogeneous group of lymphomas characterized by T and B clonal lymphoproliferative infiltrates that appear and remain confined to the skin without evidence of involvement of other organs/ systems in the six months following diagnosis.

Cutaneous T epidermotropic lymphomas subtype have a favorable response to topical treatment with steroids. Betamethasone dipropionate is a synthetic high-potency glucocorticoid with anti-inflammatory and immunosuppressive action used as a main topical therapy in early stages of NHL-T–Mycosis Fungoides, or as an adjuvant therapy in advanced stages of the disease.

In the Portuguese Pharmaceutical market just a 0.05% (w/w) cream is available although for this therapeutic indication strength should be in a range of 0.025% - 0.1% (w/w).

Table I – Set up of Formulations

Composition % (w/w)		
Betamethasone dipropionate	Active substance	0.129
Liquid Paraffin	Occlusive, emollient	28
White Soft Paraffin	Occlusive, emollient	20
Polysorbate 80 (Tween® 80)	Emulsifier agent O/W	5
Sorbitan Stearate (Span® 60)	Emulsifier agent W/O	5
Glycerol Monostearate 40-55	Thickener	5
Glycerol	Humectant	10
Purified Water	Solvent	26.9

Purpose

Study the stability during 90 days at 25 ± 2°C and 5 ± 3°C, evaluate the *in vitro* release and perform preliminary clinical studies of a topical emulsion containing Betamethasone Dipropionate 0.1% w/w for cutaneous T-cell lymphoma.

Fig. 1: Betamethasone cream's appearance

Materials and Methods

Three batches of a new formulation – a water / oil (w/p) emulsion containing betamethasone dipropionate 0.1% (w/w) have been prepared. Macroscopic analysis, pH, droplet-size distribution, rheological characterization, microbiological analysis and drug assay were assessed during 90 days.

A preliminary *in vitro* drug release has been experienced.

Preliminary clinical evaluation of skin lesions has been carried out in twenty patients.

Table II - Clinical data of 10 patients

Patient	Sex	Age	T-NHL subtipe	Stage	Begining of topical Betamethasone	1st month		2nd month		3rd month	
2	M	77	MF	II b	09-08-2012	++	PR	+++	PR	+++	PR
3	M	77	MF	I b	01-08-2012	++	PR	+++	PR	+++	PR
4	M	48	MF	I a	08-10-2012	+++	CR	+++	CR	+++	CR
5	F	59	MF	I b	29-08-2012	++	SD	++	SD	+++	SD
6	F	70	MF	IV	01-08-2012	PD		PD		died	
7	F	83	MF	I b	31-10-2012	++	PR	++	PR	+++	PR
11	M	73	MF	I b	03-09-2012	+++	PR	+++	PR	+++	PR
12	M	68	MF (Follicl.)	I a	22-08-2012	PD		PD		PD	
13	M	42	MF (Follicl.)	II b	16-07-2012	+	SD	+	SD	+	SD
14	M	53	SS	IV	10-08-2012	+	PD	+	PD	+	PD

Legend: CR - Complete Response; PR - Partial Response; SD-Stabilized Disease; PD-Progressive Disease; + < Pruritus; + < Infiltration; + < Affected area

Results and Discussion

The results obtained show that the batches prepared were physically, chemically and microbiologically stable during 90 days at both storage temperatures.

The *in vitro* release study revealed that BD released through Tuffryn® membranes.

Ten out of twenty six patients completed three months of treatment. Twelve are still under evaluation since topical betamethasone was initiated this year. Four were lost to follow up. Preliminary clinical evaluation of skin lesions showed a significative diminuition in itching, infiltration and size of plaques area.

No side effects such as skin irritation, contact dermatitis were noticed.

Conclusions

Under these experimental conditions the 3 batches resulted physically, chemically and microbiologically stable during 90 days. Nevertheless, in accordance with the results obtained, this study showed an inhomogeneity of the formulation. Indeed batch 2 always presented a different profile in many assays and it was possible to observe a high value variability in the same batch. This may be due to the preparation method, since the manually stirring may not be able to assure a good homogeneity of the drug into the emulsion, and to the quantities prepared, since it resulted very difficult to perform a proper mixing in the mortar when we prepared 500g of formulation. For a future study it would be advisable to prepare less quantities of each batch and to use an automatic mixing instead of a manually one, in order to assure a homogeneous drug distribution.

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