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Review

Rationale and evidence for the incorporation of heparin to the diclofenac epolamine medicated plaster

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Abstract

Objective: The nonsteroidal anti-inflammatory drug (NSAID) diclofenac epolamine (DHEP) formulated as a topical patch has demonstrated efficacy and safety in the localized treatment of acute pain from minor strains, sprains, and contusions, and for epicondylitis and knee osteoarthritis. The glycosaminoglycan heparin enhances the activity of topical NSAIDs formulated as a medicated plaster, even in the absence of any significant release of heparin. Therefore, DHEP Plus, a new formulation of the DHEP medicated plaster containing a small amount of heparin sodium as excipient has been developed.

Methods: We reviewed the pivotal and supportive studies of the clinical development program of the new patch and evaluated the role of heparin as an enhancer in the treatment of localized pain/inflammation of musculoskeletal structures, associated with post-traumatic and/or rheumatic conditions.

Results: The data were consistent with the concept that heparin increased the clinical activity of the DHEP Plus medicated plaster versus the reference DHEP medicated plaster through improved bioavailability due to enhanced movement of diclofenac from the plaster. Both DHEP formulations have the same dissolution profile, indicating that heparin does not change the physical and chemical characteristics of the plaster. Permeation testing showed that heparin is not released from the DHEP Plus medicated plaster. Efficacy studies showed that the DHEP Plus medicated plaster was significantly more effective in reducing pain than the reference marketed DHEP medicated plaster.

Conclusions: The benefit/risk assessment of DHEP Plus 180 mg medicated plaster is favorable, with a safety profile equal to placebo and improved efficacy over the reference marketed DHEP medicated plaster.

Short title: Development of a diclofenac epolamine medicated plaster with heparin as excipient

Keywords: nonsteroidal anti-inflammatory drugs; diclofenac epolamine patch; heparin; excipients; pain

1. Introduction

Topical formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) have been developed with the aim of reducing the systemic impact of NSAIDs. As a class, NSAIDs are associated with a number of adverse effects, including gastrointestinal complications, nephrotoxicity, and cardiovascular events[1-7]. Topical NSAID formulations are designed to deliver effective analgesic activity when locally applied while limiting systemic exposure. A recent analysis of the Cochrane Database of Systematic Reviews concluded that topical NSAIDs are safe and effective in helping to reduce pain associated with acute sprains and strains and that topical NSAIDs, specifically diclofenac and ketoprofen, may provide useful levels of pain relief in osteoarthritis[8-10]. In acute musculoskeletal pain conditions such as strains and sprains, the number needed to treat (NNT) to achieve ≥50% pain relief when used for approximately 7 days was between 1.8 and 4.7 depending on the active substance and formulation[9,11]. For chronic pain musculoskeletal conditions, predominantly hand and knee osteoarthritis, the NNT for topical diclofenac preparations was 5.0 when used for <6 weeks, 9.8 for >6–12 weeks, and 6.9 for ketoprofen gel used for >6–12 weeks[9]. Comparisons other than placebo were limited, but data from the 5 studies reviewed found that the proportion of participants achieving treatment success was 55% with topical NSAIDs and 54% with oral preparations[8]. Of interest, a recent systematic review and network meta-analysis of randomized controlled trials and observational studies of topical NSAIDs (including gels, solutions, creams, and medicated plasters) in osteoarthritis concluded that they were effective and safe for knee osteoarthritis and determined that diclofenac medicated plasters were more effective than other topical NSAID formulations[12].

There is substantive evidence, based on large, good quality trials, that topical NSAIDs reduce the incidence of systemic complications, including gastrointestinal ulceration and bleeding, compared with systemic NSAIDs[8,9,13-15]. The majority of the published evidence base for topical NSAIDs is related to formulations of diclofenac, a commonly-used NSAID which inhibits both isoforms of cyclooxygenase (COX), COX-1 and COX-2[16] and has demonstrated anti-inflammatory, analgesic and antipyretic activity resulting from the inhibition of prostaglandin synthesis[8,9,17,18].

A topical patch formulation of diclofenac epolamine (diclofenac hydroxyethylpyrrolidine, DHEP) 1.3%[19], developed by IBSA Institut Biochimique S.A. (Lugano, Switzerland) was approved for use in Europe in 1993 and in the United States (USA) in 2007 (Flector® Tissugel 1%; Flector® Patch 1.3%)[20] for symptomatic treatment of localized pain and inflammatory conditions affecting joints, muscle, tendon, and ligaments for adults and adolescents older than 16 years. This is specifically indicated for the topical treatment of acute pain from minor strains, sprains, and contusions, as well as for epicondylitis and knee OA in Europe.

The safety and efficacy of the marketed DHEP medicated plaster have been demonstrated by data from clinical studies and postmarketing experience of the treatment of acute musculoskeletal pain associated with soft tissue injuries and inflammatory pathologies, including osteoarthritis and

other rheumatological conditions[5,8,9,21-26]. Results from a skin permeability and pharmacokinetic study[10] and a pharmacokinetic study in healthy volunteers[27] show that the systemic exposure of diclofenac is very low compared with oral administration when applied as the DHEP medicated plaster. The systemic exposure to the DHEP medicated plaster at steady state, after 4 days of twice-daily application, was over 99% less than after a single oral dose of diclofenac[27]. This in accordance with the findings from a relevant animal model, which showed that penetration of diclofenac into the underlying muscle when applied as a medicated plaster was sustained and appeared to follow zero-order kinetics, while systemic bioavailability and distribution into other tissues was very limited[10]. Similar concentrations of diclofenac in the immediate tissue underlying the patch area were obtained with both topical and 50 mg oral administration of diclofenac[10].

In comparison, other studies with gel formulations of diclofenac applied to give total daily doses between 5 and 40 mg diclofenac have been shown to yield formulation-dependent plasma diclofenac concentrations ranging from approximately 1.1 to 8.2 ng/mL, which were higher than both subcutaneous and muscle diclofenac microdialysate concentrations, and were at least 150 times lower than those achieved after oral dosing[28].

Recently, topically-applied heparins, have been utilized for their anti-inflammatory properties and micro-vascular activity for prevention and the treatment of local symptoms (i.e., pain, edema) associated with peripheral vascular disorders[29].

The absorption through the skin of topical formulations may be enhanced by gentle rubbing during application of the cream or gel. Here, the absorption of heparin from the sticky poultice base of a medicated plaster is negligible. It has been postulated that heparin, as an excipient, may have other properties that enhance the activity of topical NSAIDs formulated as a medicated plaster, even in the absence of any significant release of heparin from the plaster. To exploit these effects, DHEP Plus medicated plaster (Flectormed®[1], containing DHEP 180 mg, corresponding to 140 mg diclofenac sodium) was developed as a new formulation of the reference marketed DHEP medicated plaster.

The DHEP Plus medicated plaster is identical to the marketed DHEP medicated plaster, except for the presence in the formulation of a relatively small amount of unfractionated heparin sodium of porcine origin.

This critical review summarizes the clinical development process of the DHEP Plus medicated plaster and discusses the role of heparin sodium as an enhancer in the treatment of localized pain and inflammation of musculoskeletal structures, associated with post-traumatic and/or rheumatic conditions. Published studies identified in Embase and MEDLINE (via PubMed) have been reviewed together with unpublished data on file from the clinical development program of the DHEP Plus 180 mg medicated plaster provided by IBSA Institut Biochimique S.A.

2. Characteristics of the DHEP Plus 180 mg medicated plaster

2.1 Clinical pharmacology of diclofenac epolamine

Diclofenac is a commonly used NSAID with well-established analgesic and anti-inflammatory activities resulting from the inhibition of COX-1 and COX-2 isoenzymes and reduced prostaglandin synthesis[16], but with a four-fold selectivity for COX-2[30]. Inhibition of COX-2 reduces pain and inflammation. The analgesic efficacy of diclofenac epolamine when administered topically in plaster or gel form has been demonstrated in the symptomatic treatment of various painful local conditions of different origins, such as knee osteoarthritis[31,32], localized inflammatory diseases[33], inflammatory peri- and extra-articular rheumatic diseases[34], minor sport injuries[35,36], shoulder periarthritis and lateral epicondylitis[37], peri- and extraarticular inflammatory diseases[38], sprains, strains and contusions[39].

[1] Other available tradenames include Flectorin®, Flectopar®, Flalgo®, and Weavor®.

2.2 Product development rationale

During the 1980s, IBSA together with the manufacturer Teikoku Seiyaku of Japan developed a medicated plaster containing as the active ingredient (NSAID) diclofenac epolamine (DHEP) 1.293g/100g of paste spread on an unwoven cloth. This drug product meets the definition of 'medicated plaster' in the European Pharmacopoeia[40]. The product is marketed as Flector® Tissugel 1% in Europe and Flector® Patch 1.3% in the US.

2.3 Choice of permeability enhancer

Heparin is a naturally-occurring glycosaminoglycan found in the secretory granules of mast cells in different organs, particularly the lung, liver, heart and intestinal mucosa. The choice of strength for inclusion in the medicated plaster is within the range of existing marketed topical products and based on comparative permeability studies of medicated plaster formulations of diclofenac epolamine with or without heparin as excipient performed *in vitro* with a Franz cell diffusion system using different membranes (see Comparative *in vivo* drug release and permeation profiles section).

The probable mechanism responsible for the permeability-enhancing properties of heparin has to be fully elucidated. As a polar, high molecular weight glycosaminoglycan, heparin is characterized by a high negative charge due to the presence of abundant sulfate and carboxylic groups in its structure. It is hypothesized that electrostatic repulsion forces between heparin and the less negatively charged, low molecular weight diclofenac epolamine might affect the diffusion flux of this molecule from the patch poultice through lipophilic membranes, with corresponding increased skin deposition and permeation. This behavior has been observed for other large highly-charged molecules, such as proteins, peptides, and oligonucleotides, where the charge may decrease, *in vivo*, the transepithelial electrical resistance and improve the permeation of the active ingredient[41]. However, to the best of our knowledge, these properties have not specifically been studied for heparin, and confirmation of the properties demonstrated in the DHEP Plus medicated plaster clinical development program for the role of heparin as a permeability enhancer await a suitably-designed *in vitro* study.

2.4 Development of the DHEP Plus medicated plaster

Based on the rationale of providing improved clinical efficacy compared with the first generation marketed DHEP medicated plaster, a second-generation patch, DHEP Plus medicated plaster was developed, which is identical in composition to the first except for the addition of heparin as an excipient.

2.5 Formulation of the drug product

The medicated plaster is prepared by mixing the active ingredient with a viscous base of hydrophilic polymers (such as gelatin, carmellose sodium, sodium polyacrylate and povidone), sorbitol and water. The mixed base is spread on a backing cloth, the surface is covered with polypropylene plastic film (the "release liner"), and the molded cataplasm is cut to an appropriate size. Although the composition does not contain a true adhesive, the plaster is effectively adherent because of the presence of hydrophilic polymers and sorbitol, with the result that the plaster can be simply applied on the skin of the affected area. The medicated plaster contains abundant water, allowing the drug substance to be dissolved in an aqueous phase which helps to impart a cooling effect after application. The manufacturing and distribution of the poultice are performed in two steps following the manufacturing process.

The formulation contains diclofenac epolamine as the active ingredient and a number of excipients with different roles, including viscosity enhancing agents, a chelating agent, humectants, pH buffers, preservatives (low levels of methyl- and propyl-paraben), coloring agents, fragrance and, finally but importantly, heparin as a permeability enhancing agent for the active ingredient, diclofenac epolamine. Of note, the formulation avoids the use of the solvent, dimethyl sulfoxide

(DMSO), as a permeability enhancer, thus avoiding the garlic-like smell and potential toxic effects of DMSO. The medicated plaster consists of an unwoven cloth spread with a hydrophilic paste or hydrogel poultice which is protected by a plastic film (Figure 1).

The DHEP Plus medicated plaster was developed to provide a convenient once-daily application, whereas other topical formulations of NSAIDs and heparinoids (e.g., ointments and gels) require frequent application and may adhere to clothing. In the form of a medicated plaster, the drug substance diclofenac epolamine has local analgesic and anti-inflammatory activity particularly suitable for the treatment of pain related to post-traumatic injuries of the musculoskeletal system while minimizing systemic exposure.

2.6 Comparative in vivo *drug release and permeation profiles*

Comparative *in vitro* dissolution testing of diclofenac epolamine performed according to European Pharmacopoeia protocol 2.9.4 (transdermal patches) during the development of the new formulation showed that both the DHEP Plus formulation and the reference marketed DHEP medicated plaster have the same dissolution profile. This indicates that the addition of heparin does not appear to induce any change in the physical or chemical characteristics of the plaster. The dissolution test profiles confirmed that more than 70% of diclofenac epolamine is released within 180 minutes in both drug products.

Comparison of the *in vitro* release and permeation of diclofenac epolamine from the reference marketed DHEP medicated plaster has been conducted with a Franz cell diffusion system using different membranes, and recently with the MatTek EpiDerm™ EPI-606-X System (standardized tridimensional skin surrogate models).

The permeated diclofenac epolamine was analyzed using validated analytical methods. A plot of mean Franz cell permeation profiles of diclofenac epolamine from the reference marketed DHEP medicated plaster and the DHEP Plus medicated plaster is given in Figure 2. At 24 hours, mean permeated diclofenac epolamine was 122.69 µg/cm^2 for the DHEP Plus medicated plaster, compared with 106.80 µg/cm^2 for the reference marketed DHEP medicated plaster. Analysis of bioequivalence of the cumulative amounts of diclofenac epolamine permeated at any time performed on the log-transformed data showed that the 90% confidence interval (CI) of the difference between the log-transformed data of the two products was outside the range ± 0.2231 (i.e., 80%–125% of the log of the ratio between the data of two products) at every time point (Data not shown). Thus, the cumulative amounts of diclofenac epolamine permeated for the two products cannot be considered bioequivalent; the amount of diclofenac epolamine released from the DHEP Plus medicated plaster is greater than that from the marketed DHEP medicated plaster.

Furthermore, permeation testing demonstrated that heparin is not released from the DHEP Plus medicated plaster; no heparin was detectable in the receiving chamber of the Franz Cell System used to evaluate permeation from the DHEP Plus medicated plaster under a range of test conditions.

In conclusion, the increased permeability of diclofenac through the EpiDerm EPI-606-X membranes demonstrated that heparin, added in the plaster matrix, behaves as a permeability enhancer of the active ingredient. As the activated partial thromboplastin time (aPTT) was unchanged after DHEP Plus medicated plaster application[42], confirming the absence of any heparin-related anticoagulant activity, and residual heparin content in the plaster after 24 hours of cutaneous application in another study was not different from the initial content[43], both findings support the conclusion that no heparin is released from the plaster.

2.7 Clinical pharmacological objectives

A series of studies were designed to assess specific clinical pharmacology and pharmacokinetic properties of the DHEP Plus medicated plaster (Table 1).

2.8 Pharmacokinetic studies

The pharmacokinetics of diclofenac epolamine when formulated as a medicated plaster with heparin as an excipient was investigated in three studies: Study CRO-PK-02-92[42], CRO-PK-98-13[44], and CRO-PK-12-272[43].

2.81 Study CRO-PK-02-92

Study CRO-PK-02-92 (Table 1) evaluated the percutaneous absorption of diclofenac epolamine and heparin after repeated cutaneous application in healthy volunteers[42]. Application of DHEP Plus 180 mg medicated plaster twice daily for 6 consecutive days did not produce clinically relevant changes in activated partial thromboplastin time (aPTT) values from pre-dose values at any time point, demonstrating that heparin was not absorbed in systematically effective concentrations. Mean diclofenac plasma concentrations ranged between 1.44 and 2.36 ng/mL and were approximately 500- to 1,000-times lower than the diclofenac C_{max} achieved in plasma after oral administration of diclofenac sodium at the recommended therapeutic dose[45].

2.82 Study CRO-PK-98-13

Study CRO-PK-98-13 (Table 1) was an open-label randomized, two-way crossover, multiple-dose study designed to assess the bioavailability of diclofenac by comparing the percutaneous absorption of diclofenac and heparin following application of DHEP Plus 180 mg medicated plaster and the reference marketed DHEP medicated plaster twice-daily (12-hour) for 7 days to the back of healthy volunteers at a single center[44].

Systemic exposure to diclofenac was low with both products, and there was no clinically-significant increase in systemic exposure following application of the DHEP Plus medicated plaster compared with the reference DHEP medicated plaster (Table 2). Statistical comparison of the main pharmacokinetic parameters in the final phase showed very similar bioavailability for the Test and Reference plasters (F_{rel} = 110.58 ± 46.71). Safety profiles for the two formulations were similarly satisfactory, with itching at the application site the only adverse event (AE) possibly related to the product.

2.83 Study CRO-PK-12-272

Study CRO-PK-12-272 (Table 1) was a two-part study that assessed the residual content of diclofenac epolamine and heparin in the DHEP Plus 180 mg medicated plaster after 24-hour application (Part I) and obtained data on the effects of three non-standard treatment conditions (moderate exercise, under occlusion and moderate heat exposure) on the percutaneous absorption of diclofenac following multiple applications of DHEP Plus 180 mg medicated plaster (Part II)[43]. There was no change in the residual content of heparin after 24 hours application (before 5,584.75 ± 356.35 – after 5,621.38 ± 363.46, Heparin (IU), mean ± standard deviation), demonstrating that heparin is not released from the patch and therefore available for percutaneous absorption.

In Part II, mean diclofenac plasma concentrations measured before and after the last plaster application showed that, while both rate (maximum concentration; C_{max}) and extent at steady state (AUC_T) of diclofenac absorption for the three tested conditions were higher than for the standard (resting) condition, differences in time to maximum concentration (T_{max}) values were not statistically significant (p = 0.2568). No treatment effect was observed (p = 0.0933). There was a sequence effect comprising a 10–20% increase in rate and extent of absorption for all three comparisons ($p \leq$ 0.0471), which was considered unlikely to reflect a clinically-relevant increase in systematic exposure to diclofenac, which always remained >100 times lower than after a typical 50 mg oral dose of diclofenac. The combined usage of DHEP Plus 180 mg medicated plaster with occlusive or

moderately heating wraps/bandages or the wearing of the plaster during moderate physical exercise, therefore, does not pose additional risks for patients.

2.9 Pharmacodynamic study

2.91 Affaitati, et al. 2015[46]

The primary aim of this study (Table 1) was to assess the effects of diclofenac epolamine on somatic pain sensitivity in 104 healthy asymptomatic subjects with a latent algogenic condition (hyperalgesia without spontaneous pain) of the deep tissues (subcutis and muscle) of the lower limbs after topical application of DHEP Plus 180 mg medicated plaster[46].

Both DHEP Plus 180 mg medicated plaster and DHEP medicated plaster increased the pain threshold to electrical stimulation compared with placebo, with a substantially greater increase with DHEP Plus 180 mg medicated plaster compared with the other groups over the treatment period both in the intention-to-treat (ITT) and per protocol (PP) population (Table 3). There was a 30% increase from baseline with the DHEP Plus medicated plaster, compared with 12% with the marketed DHEP medicated plaster. The results of the secondary variables (pain threshold to mechanical stimulation in muscle, and thickness of muscle at ultrasound examination) showed a trend similar to those obtained for electrical stimulation, even if they did not reach statistical significance due to the high variability observed (data not showed).

The results indicate a higher efficacy of DHEP Plus 180 mg medicated plaster over the reference DHEP medicated plaster in increasing the pain threshold to electrical stimulation at the muscle level after daily application for 7 consecutive days, suggesting that the addition of heparin to diclofenac in a patch formulation could be useful to treat pain conditions even in the absence of objective signs of injury, edema or hematoma.

2.10 Pharmacology conclusions

The pharmacokinetic and pharmacodynamic data are collectively consistent with the concept that the presence in the formulation of a small amount of heparin enhances the clinical activity of DHEP Plus 180 mg medicated plaster compared with the reference DHEP medicated plaster[46]. However, since heparin is entrapped in the plaster poultice, as shown by the lack of heparin release in the *in ex vivo* permeation studies and of any modification in heparin content in plasters after 24 hours of *in vivo* application (Study CRO-PK-12-272)[43], the enhanced activity is not due to a direct effect of heparin on local pain and inflammation, but instead to the enhanced release of diclofenac from the poultice, resulting in greater local bioavailability of the active drug[47].

The extent of this increase is insufficient to alter the systemic exposure of patients to diclofenac following DHEP Plus 180 mg medicated plaster when compared with DHEP medicated plaster (Study CRO-PK-02-92 and Study CRO-PK-98-13)[42,44]. Consequently, the decision to include heparin in the formulation as an excipient in the product development of the DHEP Plus 180 mg medicated plaster, with the unique role of enhancer of diclofenac, can be considered consistent with the evidence from the above studies. The probable mechanism through which heparin enhances the effects of topical diclofenac has been hypothesized to be that, since heparin is a large (≈10,000 Daltons), highly electronegative, presumably immobile molecule uniformly distributed throughout the adhesive/sticky plaster matrix, it may act by increasing the diffusibility of the much smaller, negatively-charged active ingredient via repulsive forces.

3. Clinical efficacy studies

Three pivotal studies[48-50] have investigated the efficacy of the DHEP Plus 180 mg medicated plaster

in humans. Two of these studies were conducted with the objective of showing the superiority of DHEP Plus over the reference DHEP mg medicated plaster in reducing pain on movement at Day 3 compared with baseline (primary efficacy objective)[48,49], while the third also assessed pain on active mobilization as a secondary endpoint, to confirm the superiority of DHEP Plus 180 mg medicated plaster over placebo[50]. A summary of the characteristics and design of the pivotal clinical trials is presented in Table 4.

The efficacy and safety assessments used in these studies were standard, widely used and recognized as reliable, accurate, relevant to both the tested treatments and the medical condition, and able to discriminate between effective and ineffective products. Sample sizes were calculated to demonstrate appropriate differences between groups, based on results from previously conducted trials of the reference DHEP mg medicated plaster with very similar study designs. It should be emphasized that, although designed to use similar outcome measures, there was inevitably some heterogeneity in patient populations and dose regimens in these studies, and it is not intended that direct comparisons of efficacy be made between studies.

Pain on movement as a primary efficacy criterion was based on clinical relevance in relation to the population/conditions under investigation (ankle sprain, muscle contusion), and analyzed using the 0–100 mm Visual Analog Scale [VAS]), the latter a validated, reproducible, commonly used index of pain. In addition, the use of pain on movement as a primary criterion for the evaluation of drug activity is recommended by current regulatory and scientific guidelines (European Medicines Agency [EMEA] documents CPMP/EWP/784/97 Rev. 1, 23 July 1998, and CPMP/EWP/612/00, 21 November 2002).

A further non pivotal study investigated the time to complete hematoma dissolution and pain parameters in patients with mild-to-moderate muscle contusions and strains (Table 4)[51].

Overall, the phase III studies, which enrolled patients suffering from minor post-traumatic injuries, consistently found that DHEP Plus 180 mg medicated plaster was significantly more effective in reducing pain than the DHEP medicated plaster or vehicle (placebo plaster) (Table 5)[48-51]. Both active formulations were also significantly more effective than placebo. In DHEP medicated plaster recipients across all the randomized-controlled trials, the mean number of applied patches per patient was 10.0 ± 3.3, treatment compliance issues were noted in only 2.3% of patients, and there were no cases of incorrect plaster application recorded.

Overall, analysis of the analgesic effects of DHEP Plus 180 mg medicated plaster (VAS score reductions in pain on movement) in the pivotal studies suggests comparable to superior efficacy to other topical NSAIDs based on results of double-blind, randomized, placebo-controlled clinical trials published in the medical literature (Figure 3), although definitive conclusions cannot be made in the absence of specific inter-drug comparisons.

Results reported in the three pivotal studies for DHEP Plus 180 mg medicated plaster show a VAS reduction ranging from 9.4 to 14.7 mm on a 0–100 mm scale, compared with placebo patients after 7 days of treatment, which can be regarded as an acceptable therapeutic outcome within the topical NSAID class. Furthermore, the mean reduction of VAS ranging between 4.9 and 7.1 mm achieved with DHEP Plus 180 mg medicated plaster compared with the DHEP medicated plaster in the same studies is at least comparable, and in some cases higher, than those obtained with other NSAIDs when compared with placebo.

3.1 Costantino et al. 2011

The primary aim of this study[48] (Table 4) was to compare the efficacy of DHEP Plus 180 mg medicated plaster with the reference marketed DHEP medicated plaster in the treatment of acute, mild-to-moderate ankle sprain involving the external lateral ligaments.

DHEP Plus 180 mg medicated plaster was significantly more effective than DHEP medicated plaster in the relief of ‘pain on movement’ after 3 days of treatment (Table 5), as well as over the

entire 7-day treatment period. Both DHEP Plus 180 mg medicated plaster and DHEP medicated plaster were significantly more effective than placebo (Table 5).

DHEP Plus 180 mg medicated plaster and the marketed DHEP medicated plaster produced a significantly greater relief in terms of 'spontaneous pain at rest' and of 'pain while leaning on the injured limb only', as compared with placebo. In addition, patients treated with DHEP Plus 180 mg medicated plaster consumed fewer tablets of rescue medication (paracetamol) than did patients treated with DHEP and placebo.

Overall, the Investigator's and patient's opinion on efficacy favored DHEP Plus 180 mg medicated plaster as compared with DHEP and placebo.

3.2 Hoffmann et al. 2012

The objective of this study[49] (Table 4) was to investigate if the DHEP Plus 180 mg medicated plaster was significantly more effective than the reference DHEP medicated plaster for pain reduction in patients with mild-to-moderate contusions with the presence of hematoma. Other objectives included pain on movement assessed daily throughout the 2-week treatment period, the presence of a superficial hematoma and time needed to reach a complete hematoma disappearance, and local and general safety.

DHEP Plus medicated plaster was significantly more effective at reducing pain on Day 3 in the primary analysis (Table 5). Pain on movement (VAS), as assessed by patients, improved faster in the DHEP Plus 180 mg medicated plaster group, compared with DHEP medicated plaster and placebo plaster (Figure 4). Overall statistical efficacy analyses confirmed the superiority of DHEP Plus 180 mg medicated plaster over the other two groups; it can be concluded that DHEP Plus 180 mg medicated plaster is significantly more effective than DHEP medicated plaster in relieving pain from recent mild-to-moderate muscle contusions when applied daily for as long as 14 days. Both DHEP Plus 180 mg medicated plaster and DHEP medicated plaster were proven to be significantly more effective than a placebo plaster, while showing a comparably favorable, placebo-like local and general safety profile.

3.3 Coudreuse and De Valthaire 2010

The following study[50] (Table 4) compared the efficacy and tolerability of DHEP Plus 180 mg medicated plaster with placebo for the treatment of painful minor lateral ankle sprain with perimalleolar edema.

Patients treated with DHEP Plus 180 mg medicated plaster experienced a nearly significantly greater reduction of edema within the first 3 days ($p = 0.06$)) compared with placebo, reaching significance after seven days of treatment ($p = 0.003$. ANOVA analysis for the evolution of the perimalleolar edema over the entire 7-days period showed a significantly superior treatment effect for the DHEP Plus 180 mg medicated plaster group ($p = 0.01$).

The DHEP Plus 180 mg medicated plaster also reduced spontaneous pain significantly more effectively than placebo (Table 5) at all post-treatment evaluation time points (data not shown) except at 2 and 5 hours, despite higher pain at inclusion ($p = 0.01$) in patients in the active plaster group. At the end of treatment period, global judgment of treatment efficacy by physicians was in favor of DHEP Plus 180 mg medicated plaster compared with placebo ($p < 0.05$); the effectiveness of treatment was judged to be good-to-excellent in 85% of DHEP Plus 180 mg medicated plaster- and in 70% of placebo-treated patients.

The results confirmed that once-daily application (for 24 hours) of DHEP Plus 180 mg medicated plaster in double-blind conditions was superior to placebo (vehicle) in controlling and reducing pain and counteracting joint swelling in patients suffering from a mild-to-moderate sprain of the external lateral ligament of the ankle.

3.4 Klainguti et al. 2010

The primary aim of the non-pivotal study[51] (Table 4) was to assess the time to complete hematoma resolution in patients with mild-to-moderate muscle contusions and strains accompanied by superficial hematoma and spontaneous pain. Pain on movement and pain at rest were also assessed.

Starting from Day 4 of treatment and throughout the entire treatment period, patients treated with DHEP Plus 180 mg medicated plaster had a cumulative rate of hematoma resolution significantly higher than those receiving either DHEP medicated plaster or placebo (between-group difference $p < 0.05$, for both comparisons). Cox's proportional hazards regression analysis showed that there was a significantly higher likelihood of successful hematoma dissolution with DHEP Plus 180 mg medicated plaster than DHEP medicated plaster ($p = 0.03$) and placebo ($p = 0.02$), representing a 62% greater chance of achieving complete hematoma dissolution within 10 treatment days with DHEP Plus 180 mg medicated plaster.

According to patient self-ratings, significantly greater reductions in pain on movement were reported in the DHEP Plus 180 mg medicated plaster and in the DHEP group (data not shown) compared with the placebo group after 2 and 3 days of treatment (Table 5).

The total amount of rescue medication consumed by patients in the placebo group during the first three treatment days was higher than in patients treated with DHEP Plus 180 mg medicated plaster or DHEP medicated plaster.

The results demonstrate that the DHEP Plus 180 mg medicated plaster is more effective than the reference marketed DHEP medicated plaster in fostering hematoma resolution frequently associated with mild-to-moderate sports-related injuries, but not with regard to pain management if treatment is limited to 12 hours per day.

3.5 Comparative outcomes (number needed to treat)

In the clinical efficacy studies that assessed analgesic effects in terms of reduction of pain on movement[48-50], a higher proportion of patients treated with the DHEP Plus medicated plaster compared with placebo achieved success (defined as ≥50% reduction of pain on movement as assessed by the patient on a VAS of 0-100 mm) after 3 or 7 days of once-daily plaster application (Table 6). For the DHEP Plus medicated plaster, the NNT for one patient to achieve clinical success was 4.00 after 7 days of treatment (95% CI 3.04–5.83) (Table 6).

4. Safety

The DHEP Plus 180 mg medicated plaster was developed as a formulation identical to that of the reference marketed DHEP medicated plaster, except for the presence of a small amount of unfractionated heparin sodium per medicated plaster. As *in vitro* permeation studies[47], and *in vivo* pharmacodynamic[43] and pharmacokinetic studies[42,44] have demonstrated that heparin is not released from the plaster, and very low amounts of diclofenac are systemically distributed after topical application of the DHEP Plus medicated plaster, the safety of the DHEP Plus 180 mg medicated plaster was expected to be similar to that of the marketed DHEP medicated plaster; i.e. any tolerability issues were expected to be local skin reactions at the application site.

Safety and tolerability data collected in Studies CRO-PK-02-92, EU01.2002 and 13FCDN-FHp03[42,52,53] also demonstrated excellent local tolerability of the DHEP Plus medicated plaster, with very low irritation scores that were superimposable with those of the marketed DHEP medicated plaster or placebo and with no apparent hypersensitization reactions.

4.1 Adverse events in the clinical trials

In the phase III clinical trials (Table 4), all AEs that occurred during the study period (from enrollment and throughout the whole treatment period) of the phase III placebo- and/or active-controlled clinical trials, irrespective of their relation to treatment were to be reported by the Investigator in

the patient's case report form, and were to be followed up if necessary until resolution or up to 4 weeks after the end of the treatment period. The nature, seriousness, and intensity of the AE, as well as and their correlation with the treatment received, were recorded. Additionally, patients were instructed to record any untoward effects suffered over the course of the study in their diaries, irrespective of their perceived relationship to treatment. At each control visit, the investigator monitored AEs and patient diaries were reviewed by the doctor during clinic visits.

The most frequently observed AEs following treatment with DHEP Plus 180 mg medicated plaster were cutaneous AEs at the plaster application site, including pruritis, irritation, rash, edema and warmth. These reactions occurred at similar rates among all treatment groups (Table 7), and of the few systemic AEs reported in the trials, none were considered to be related to treatment.

No new safety concerns related to the DHEP Plus medicated plaster were identified.

4.2 Drug interactions and special considerations

Due to the very low levels of systemic absorption of diclofenac from the DHEP Plus 180 mg medicated plaster and following the experience with the marketed DHEP medicated plaster, no interaction with other concomitant drugs has been observed or is expected to be observed in post-marketing use. Data to support the use of DHEP Plus 180 mg medicated plaster in pregnancy or lactation are lacking. Consequently, as a precaution, DHEP Plus 180 mg medicated plaster must not be used during the first and second trimester of pregnancy and it is contraindicated starting from the sixth month of pregnancy, and the medicated plaster should only be used during lactation under advice from a healthcare professional.

Following the recommendations released for the use of systemic and topical formulations of diclofenac in pediatric populations contained in the Public Paediatric Assessment Report (DE/W/001/pdWS/001), it is intended that the use of DHEP Plus 180 mg medicated plaster should be limited to patients 16 years of age or older.

5. Benefit / risk overview and conclusions

DHEP Plus 180 mg medicated plaster was found to be significantly more effective in reducing pain than the reference marketed DHEP medicated plaster in the two pivotal phase III studies enrolling patients suffering from minor post-traumatic injuries, with both active formulations also being significantly more effective than placebo[48,49]. Therefore, a claim for the new formulation to be used for the treatment of localized pain and inflammation of muscle-skeletal structures, associated with post-traumatic and/or rheumatic conditions, seems to be adequate and justified.

The DHEP Plus 180 mg medicated plaster is applied as a once-daily dose regimen, which is very convenient for the patient, with a recommended maximum 14-day treatment duration. The clinical trial program showed that compliance with the DHEP Plus medicated plaster is excellent, and an absence of incorrect application of the plasters supports the convenience and ease of use of the product. However, as with all active pharmaceutical products, DHEP Plus medicated plasters should be used with appropriate regard to the indication, with dosage and application instructions consistent with individual patient treatment goals.

The data generated during the clinical development program are collectively consistent with the concept that the role of heparin in the increased clinical activity of DHEP Plus 180 mg medicated plaster in comparison to the reference DHEP medicated plaster is not due to a direct effect of this highly sulfated glycosaminoglycan on local pain and inflammation, but to the enhanced movement of the diclofenac from the poultice, improving local tissue bioavailability of the active ingredient. Therefore, the decision to include heparin in the formulation would seem to be adequately justified.

Moreover, the new DHEP Plus medicated plaster appears to be characterized by a placebo-like safety profile, with minor local skin reactions at the site of application being the only medically relevant events.

DHEP Plus medicated plaster with the presence of heparin as permeability enhancer, on the basis of all the available scientific evidence, thus represents a new and effective therapeutic option for the local symptomatic treatment of acute minor painful musculoskeletal conditions (i.e. affecting joints, muscle, tendon and ligaments), with a positive benefit/risk profile.

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References

1. Graham DJ. COX-2 inhibitors, other NSAIDs, and cardiovascular risk: the seduction of common sense. JAMA 2006;296(13):1653-6
2. Ong CK, Lirk P, Tan CH et al. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res 2007;5(1):19-34
3. Costantini R, De Nicola P, Bianco F et al. Tumor vs non-tumor origin of occult and obscure gastrointestinal bleeding requiring hospitalization. Tumori 2007;93(5):461-6
4. Garcia Rodriguez LA, Hernandez-Diaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. Arthritis Res 2001;3(2):98-101
5. McCarberg BH, Argoff CE. Topical diclofenac epolamine patch 1.3% for treatment of acute pain caused by soft tissue injury. Int J Clin Pract 2010;64(11):1546-53
6. Rainsford KD. Anti-inflammatory drugs in the 21st century. Subcell Biochem 2007;42:3-27
7. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 1999;340(24):1888-99
8. Derry S, Conaghan P, Da Silva JA et al. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2016;4:CD007400
9. Derry S, Wiffen PJ, Kalso EA et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. Cochrane Database Syst Rev 2017;5:CD008609
10. Tse S, Powell KD, Maclennan SJ et al. Skin permeability and pharmacokinetics of diclofenac epolamine administered by dermal patch in Yorkshire-Landrace pigs. Journal of pain research 2012;5:401-8
11. Derry S, Wiffen P, Moore A. Topical nonsteroidal anti-inflammatory drugs for acute musculoskeletal pain. JAMA 2016;315(8):813-4
12. Zeng C, Wei J, Persson MSM et al. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies. Br J Sports Med 2018;52(10):642-50
13. Altman RD, Barthel HR. Topical therapies for osteoarthritis. Drugs 2011;71(10):1259-79
14. Petersen B, Rovati S. Diclofenac epolamine (Flector) patch: evidence for topical activity. Clin Drug Investig 2009;29(1):1-9

15. Roth SH. Coming to terms with nonsteroidal anti-inflammatory drug gastropathy. Drugs 2012;72(7):873-9
16. Schwartz JI, Dallob AL, Larson PJ et al. Comparative inhibitory activity of etoricoxib, celecoxib, and diclofenac on COX-2 versus COX-1 in healthy subjects. J Clin Pharmacol 2008;48(6):745-54
17. Gan TJ. Diclofenac: an update on its mechanism of action and safety profile. Curr Med Res Opin 2010;26(7):1715-31
18. Brogden RN, Heel RC, Pakes GE et al. Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. Drugs 1980;20(1):24-48
19. Rainsford KD, Kean WF, Ehrlich GE. Review of the pharmaceutical properties and clinical effects of the topical NSAID formulation, diclofenac epolamine. Curr Med Res Opin 2008;24(10):2967-92
20. Flector - diclofenac epolamine topical patch 1.3%: Prescribing Information. Bristol, TN: King Pharmaceuticals Inc 2010
21. Lionberger DR, Joussellin E, Yanchick J et al. Pooled analysis of clinical trial data evaluating the safety and effectiveness of diclofenac epolamine topical patch 1.3% for the treatment of acute ankle sprain. Open Access J Sports Med 2011;2:75-84
22. Kuehl K, Carr W, Yanchick J et al. Analgesic efficacy and safety of the diclofenac epolamine topical patch 1.3% (DETP) in minor soft tissue injury. Int J Sports Med 2011;32(8):635-43
23. Gimbel J, Jacobs D, Pixton G et al. Effectiveness and safety of diclofenac epolamine topical patch 1.3% for the treatment of acute pain due to back strain: an open-label, uncontrolled study. Phys Sportsmed 2011;39(1):11-8
24. Brewer AR, Pierchala LA, Yanchick JK et al. Gastrointestinal tolerability of diclofenac epolamine topical patch 1.3%: a pooled analysis of 14 clinical studies. Postgrad Med 2011;123(4):168-76
25. Lionberger DR, Lanzarotti A, Pierchala L et al. Analgesic efficacy and safety of diclofenac epolamine topical patch (Flector® patch) by location of injury in trials of acute pain: A pooled analysis of five trials. J Appl Res 2010;10(3):97-107
26. Lionberger DR, Brennan MJ. Topical nonsteroidal anti-inflammatory drugs for the treatment of pain due to soft tissue injury: diclofenac epolamine topical patch. Journal of pain research 2010;3:223-33
27. Rusca A, Mautone G, Sun S et al. Comparison of plasma pharmacokinetics of FLECTOR® Patch (diclofenac epolamine topical patch) and oral Voltaren® (diclofenac sodium enteric coated tablets) in healthy volunteers. [Abstract no. 279]. J Pain 2008;9(4 Suppl 1):45
28. Brunner M, Davies D, Martin W et al. A new topical formulation enhances relative diclofenac bioavailability in healthy male subjects. Br J Clin Pharmacol 2011;71(6):852-9
29. Vecchio C, Frisinghelli A. Topically applied heparins for the treatment of vascular disorders : a comprehensive review. Clin Drug Investig 2008;28(10):603-14
30. Warner TD, Giuliano F, Vojnovic I et al. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci U S A 1999;96(13):7563-8
31. Brühlmann P, Michel BA. Topical diclofenac patch in patients with knee osteoarthritis: a randomized, double-blind, controlled clinical trial. Clin Exp Rheumatol 2003;21(2):193-8
32. Brühlmann P, de Vathaire F, Dreiser RL et al. Short-term treatment with topical diclofenac epolamine plaster in patients with symptomatic knee osteoarthritis: pooled analysis of two randomised clinical studies. Curr Med Res Opin 2006;22(12):2429-38
33. Rosenthal M, Bahous I. A controlled clinical study on the new topical dosage form of DHEP plasters in patients suffering from localized inflammatory diseases. Drugs Exp Clin Res 1993;19(3):99-105

34. Galeazzi M, Marcolongo R. A placebo-controlled study of the efficacy and tolerability of a nonsteroidal anti-inflammatory drug, DHEP plaster, in inflammatory peri- and extra-articular rheumatological diseases. Drugs Exp Clin Res 1993;19(3):107-15
35. Galer BS, Rowbotham M, Perander J et al. Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. J Pain Symptom Manage 2000;19(4):287-94
36. Jenoure P, Segesser B, Luhti U et al. A trial with diclofenac HEP plaster as topical treatment in minor sport injuries. Drugs Exp Clin Res 1993;19(3):125-31
37. Spacca G, Cacchio A, Forgacs A et al. Analgesic efficacy of a lecithin-vehiculated diclofenac epolamine gel in shoulder periarthritis and lateral epicondylitis: a placebo-controlled, multicenter, randomized, double-blind clinical trial. Drugs Exp Clin Res 2005;31(4):147-54
38. Fioravanti A, Cicero MR, Nerucci F et al. Double-blind controlled clinical study of the efficacy and tolerability of diclofenac-N-(2-hydroxyethyl)-pyrrolidine lecithin gel compared with diclofenac-N-(2-hydroxyethyl)-pyrrolidine gel in patients with peri and extraarticular inflammatory diseases. Drugs Exp Clin Res 1999;25(5):235-40
39. Mahler P, Mahler F, Duruz H et al. Double-blind, randomized, controlled study on the efficacy and safety of a novel diclofenac epolamine gel formulated with lecithin for the treatment of sprains, strains and contusions. Drugs Exp Clin Res 2003;29(1):45-52
40. European Pharmacopoeia 9.0. Chondroitin sulphate sodium. 01/2017:2064. 2017;
41. Naik A, Kalia YN, Guy RH. Transdermal drug delivery: overcoming the skin's barrier function. Pharm Sci Technolo Today 2000;3(9):318-26
42. IBSA Institut Biochimique SA Lugano Switzerland. Data on file. Study CRO-PK-02-92: Safety evaluation of a new transdermal plaster containing DHEP and heparin sodium; 2003.
43. IBSA Institut Biochimique SA Lugano Switzerland. Data on file. Study CRO-PK-12-272: Diclofenac PK profile after standardised exercise, plaster occlusion and moderate heat, as compared with normal (rest) conditions, and evaluation of DHEP and heparin residual content in DHEP Plus plaster after 24-h application; 2013.
44. IBSA Institut Biochimique SA Lugano Switzerland. Data on file. Study CRO-PK-98-13: BA/BE study of a new topical formulation of DHEP plaster containing heparin vs. the marketed formulation Flector EP Tissugel(R) in male and female healthy volunteers; 1998.
45. Assandri A, Canali S, Giachetti C. Local tolerability and pharmacokinetic profile of a new transdermal delivery system, diclofenac hydroxyethylpyrrolidine plaster. Drugs Exp Clin Res 1993;19(3):89-95
46. Affaitati G, Fabrizio A, Frangione V et al. Effects of topical diclofenac plus heparin (DHEP+H plaster) on somatic pain sensitivity in healthy subjects with a latent algogenic condition of the lower limb. Pain Pract 2015;15(1):58-67
47. IBSA Institut Biochimique SA Lugano Switzerland. Data on file. DRT-18.125.275b: Flector-heparin patch vs Flector patch: comparison of diclofenac epolamine permeation through EPIDERMTM MatTek membrane.
48. Costantino C, Kwarecki J, Samokhin AV et al. Diclofenac epolamine plus heparin plaster versus diclofenac epolamine plaster in mild to moderate ankle sprain: a randomized, double-blind, parallel-group, placebo-controlled, multicentre, phase III trial. Clin Drug Investig 2011;31(1):15-26
49. Hoffmann P, Kopačka P, Gugliotta B et al. Efficacy and tolerability of DHEP-heparin plaster in reducing pain in mild-to-moderate muscle contusions: a double-blind, randomized trial. Curr Med Res Opin 2012;28(8):1313-21
50. Coudreuse JM, de Vathaire F. Effect of a plaster containing DHEP and heparin in acute ankle sprains with oedema: a randomized, double-blind, placebo-controlled, clinical study. Curr Med Res Opin 2010;26(9):2221-8
51. Klainguti A, Forgacs A, Berkes I et al. A plaster containing DHEP and heparin for mild to moderate contusions and sprains with haematoma: a double-blind randomized study. Curr Med Res Opin 2010;26(9):2243-51

52. IBSA Institut Biochimique SA Lugano Switzerland. Data on file. Study EU01.2002: DHEP / Heparin Tissugel: study on the skin irritation and sensitization potential ('human repeated insult patch test' - RIPT); 2003.
53. IBSA Institut Biochimique SA Lugano Switzerland. Data on file. Study 13FCDN-FHp03: Skin irritation and sensitization evaluation of Flector(R) Plus patch: a phase I, 'repeated insult patch test' (RIPT) investigation to support the safety and tolerability of the medicated plaster (patch) formulation, in human healthy volunteers; 2003.
54. Campbell J, Dunn T. Evaluation of topical ibuprofen cream in the treatment of acute ankle sprains. J Accid Emerg Med 1994;11(3):178-82
55. Dreiser RL. Topical antirheumatic drug therapy: current practice and future trends. Eur J Rheumatol Inflamm 1994;14(4):3-8
56. Mazières B, Rouanet S, Velicy J et al. Topical ketoprofen patch (100 mg) for the treatment of ankle sprain: a randomized, double-blind, placebo-controlled study. Am J Sports Med 2005;33(4):515-23
57. Mueller EA, Kirch W, Reiter S. Extent and time course of pain intensity upon treatment with a topical diclofenac sodium patch versus placebo in acute traumatic injury based on a validated end point: post hoc analysis of a randomized placebo-controlled trial. Expert Opin Pharmacother 2010;11(4):493-8
58. Russell AL. Piroxicam 0.5% topical gel compared to placebo in the treatment of acute soft tissue injuries: a double-blind study comparing efficacy and safety. Clin Invest Med 1991;14(1):35-43

Tables

Table 1 Clinical pharmacology, pharmacokinetic and pharmacodynamic studies.

Study ID	Study design and assessments	Objective	Test products; dose regimen; route of administration	Subjects, *N*
Study CRO-PK02-92[42]	Open-label, single center study. aPTT measured pre-dose and 6 hours post-dose during daily application and at specified intervals on the last application day. Diclofenac plasma concentrations measured at specified intervals on days 1, 5, and 6.	To evaluate the risk of epicutaneous absorption of heparin sodium after repeated application of the new medicated plaster using aPTT values (a marker for the systemic absorption of heparin) and plasma concentrations of diclofenac.	DHEP Plus 180 mg medicated plaster bid on the back for 6 consecutive days.	Healthy male & female volunteers (n = 12)
Study CRO-PK-98-13[44]	Open-label, randomized, two-way crossover, multiple dose study. Blood samples were obtained on Day 8 (Period 1) and Day 22 (Period 2) pre-dose and at 12 pre-specified times until 24 hours post-dose.	To assess the systemic bioavailability and bioequivalence of DHEP Plus 180 mg medicated plaster and DHEP medicated plaster after repeated epicutaneous administration.	a) DHEP Plus 180 mg medicated plaster, b) DHEP medicated plaster bid to the right lumbar region for 7 consecutive days plus once on Day 8 with a 7-day washout period between each study period.	Healthy male & female volunteers Phase 1 (preliminary) (n = 4) Phase 2 (final) (n = 18, 16 analysed)
Study CRO-PK-12-272[43]	Open-label, single center, four-way crossover, controlled study. Diclofenac plasma pharmacokinetic parameters were measured according to validated analytical methods.	1) To assess the residual content of diclofenac epolamine and heparin in DHEP Plus medicated plaster after 24 hours of application. 2) To assess the impact of exercise, occlusion and heat on diclofenac absorption and systemic bioavailability following repeated plaster application.	1) Cutaneous application of one DHEP Plus medicated plaster for 24 hours to the inner upper part of each arm. 2) Single cutaneous application of DHEP Plus 180 mg medicated plaster od to the front thigh for 4 consecutive days in each of the 4 conditions (resting; moderate exercise; application under an occlusive bandage;	1) Healthy volunteers (n = 24) 2) Healthy volunteers (n = 14, 13 analysed)

			exposure to moderate heat) with a ≥5-day washout period between each study period.	
Study 07I/FHp04[46]	Prospective, single center, double-blind, randomized, 4-arm parallel group, controlled study. Pain thresholds to pressure and electrical standardized stimulation were measured at the level of the vastus lateralis muscle and overlying area using a Fischer's algometer (pressure pain threshold) and a computerized, constant-current, electrical stimulator.	Primary: to assess the effects of diclofenac on pain thresholds to electrical stimulation of the cutis, subcutis, and muscle when topically applied as DHEP Plus 180 mg medicated plaster in asymptomatic subjects with a latent algogenic condition (e.g., from previous knee micro-traumatic events or latent myofascial trigger points).	a) DHEP Plus 180 mg medicated plaster b) DHEP medicated plaster c) Heparin plaster (i.e., the vehicle of DHEP Plus 180 mg medicated plaster) d) Placebo plaster, od to the cutaneous area overlying the vastus lateralis muscle for 7 consecutive days.	104 (4 groups of 26) subjects (84 women, 20 men, mean age 42.2 ± 13.3 years), with deep somatic hyperalgesia in one thigh based on standardized electrical stimulation measurements.

Abbreviations: aPTT, activated partial thromboplastin time; bid, twice-daily; od, once-daily.

Table 2 Pharmacokinetic parameters of diclofenac epolamine in healthy volunteers (*n* = 16).

	DHEP Plus 180 mg medicated plaster	DHEP medicated plaster
Css_{max}, ng/mL	3.51 ± 2.04	3.59 ± 2.09
Css_{min}, ng/mL	1.20 ± 0.57	1.23 ± 0.56
Tss_{max}, hours	3.66 ± 3.88	2.16 ± 1.85
AUCss, mg/mL•h	23.42 ± 11.93	22.48 ± 10.44

Values are mean ± standard deviation.
Abbreviations: AUCss, area under the concentration/time curve at steady state; Css_{max}/Css_{min} maximum/minimum plasma concentration at steady state; Tss_{max}, time to reach maximum plasma value.

Table 3 Adjusted mean values for change from baseline of pain threshold to electrical muscle stimulation (mA) of muscle as compared to the mean values without adjustment for the covariates[46].

Plaster	DHEP Plus	DHEP	Heparin	Placebo
Day 4 (Mean ± SD)	0.29 ± 0.38	0.15 ± 0.27	0.06 ± 0.33	-0.09 ± 0.43
Day 4 (Adjusted mean for gender)	0.27	0.13	0.03	-0.12
Day 4 (Adjusted mean for subcutis thickness)	0.28	0.15	0.06	-0.09
Day 8 (Mean ± SD)	0.40 ± 0.46*†	0.16 ± 0.38‡	0.06 ± 0.38	-0.02 ± 0.28
Day 8 (Adjusted mean for gender)	0.38	0.14	0.03	-0.04
Day 8 (Adjusted mean for subcutis thickness)	0.40	0.17	0.06	0.00

*p = 0.0307 vs. the reference DHEP medicated plaster. †p = 0.002 and p < 0.0001, respectively, vs. Heparin plaster and placebo plaster. ‡p = 0.0299 vs Placebo

Table 4 Characteristics and design of the clinical trials program in the development of the DHEP Plus 180 mg medicated plaster.

Study ID	Study design / type of control	Objectives	Test products; dose regimen; route of administration	Subjects, *N*	Patient diagnoses
Pivotal studies					
Study 06EU-FHp03[48]	Multicenter (13 sites), multinational (Italy, Poland, Ukraine), prospective, double-blind, vs. active and placebo-controlled, 3-arm parallel group randomized clinical study. Assessments at clinic scheduled at inclusion (Day 1), and after 3, and 7 days, plus daily patient evaluations at home (diary), and follow-up (phone) contact on day 14.	Primary: to demonstrate that DHEP Plus 180 mg > DHEP medicated plaster in terms of reduction of pain on movement. Secondary: to demonstrate that DHEP Plus 180 mg and DHEP medicated plaster > Placebo, in pain reduction, rescue medication consumption, edema extension, pain at rest, pain while leaning on the injured limb, overall treatment efficacy. Safety: local (cutaneous) tolerability, local and systemic safety (AEs).	a) DHEP Plus medicated plaster, 1 plaster/day b) DHEP medicated plaster, 1 plaster/day c) Placebo, 1 plaster/day topically applied on the most painful area during 7 days	a) 142 / 142 b) 146 / 142 c) 142 / 140	Outpatients with acute **ankle sprain**, involving the external lateral ligament, occurred <48 hours before inclusion; sprain severity grade I or II; untreated; pain on movement ≥ 50 mm (VAS); presence of peri-malleolar edema.

Study 05DCZ-FHp11[49]	Multicenter (20 sites), multinational (Germany, Czech Republic), prospective, double-blind, vs. active and placebo-controlled, 3-arm parallel group randomized clinical study. Assessments at clinic scheduled at inclusion (Day 1), and after 7 and 14 days, plus daily patient evaluations at home (diary).	Primary: to demonstrate that DHEP Plus 180 mg > DHEP medicated plaster in terms of reduction of pain on movement. Secondary: to demonstrate that DHEP Plus 180 mg and DHEP medicated plaster > placebo in pain reduction, rescue medication consumption, bruising extension, pain at rest, overall treatment efficacy. Safety: local (cutaneous) tolerability, local and systemic safety (AEs).	a) DHEP Plus medicated plaster, 1 plaster/day b) DHEP medicated plaster, 1 plaster/day c) Placebo, 1 plaster/day topically applied on the most painful area during 14 days	a) 121 / 121 b) 115 / 115 c) 119 / 118	Outpatients with unilateral mild-to-moderate **muscle contusion of upper or lower limbs**, occurred <72 hours from inclusion, pain on movement ≥50 mm (VAS), presence of superficial hematoma (bruising).

Study 18-12-98[50]	Multicenter (18 French sites), prospective, double-blind, vs. placebo-controlled, 2-arm parallel group randomized clinical study. Assessments at clinic scheduled at inclusion (Day 1), and after 3, and 7 days, plus daily patient evaluations at home (diary): every hour during the 6 hours following the 1st plaster application, morning, noon and evening the 2nd and 3rd day.	Primary: to demonstrate the efficacy and the safety of DHEP Plus 180 mg *vs*. Placebo in terms of perimalleolar edema reduction. Secondary: to demonstrate the efficacy and the safety of DHEP Plus 180 mg vs. Placebo in terms of pain on movement (VAS), at rest, on pressure reduction, rescue medication consumption, overall treatment efficacy. Safety: local (cutaneous) tolerability, local and systemic safety (AEs).	a) DHEP Plus medicated plaster, 1 plaster/day b) Placebo, 1 plaster/day topically applied on the most painful area during 7 days	a) 120 / 117 b) 120 / 117	Outpatients with painful, minor **ankle sprain** involving the external lateral ligament, occurred <48 hours before inclusion; untreated; pain on movement ≥ 50 mm (VAS); presence of peri-malleolar edema (difference of ≥ 20 mm in submalleolar perimeter vs. the healthy ankle.
Non-pivotal study					

Study 99CH/FHp02[51]	Multicenter (18 sites in Switzerland, Hungary and Italy), prospective, double-blind, vs. placebo-controlled, 3-arm parallel group randomized clinical study. Swelling assessed at clinic at inclusion (Day 1) and evaluated by the patients every evening and the investigator at follow-up visits after 3 and 10 days using a 4-point severity scale.	Primary: time to complete hematoma dissolution. Secondary: Pain on movement (VAS) and pain at rest (VAS) for DHEP Plus 180 mg vs. DHEP medicated plaster vs. Placebo. Safety: local (cutaneous) tolerability, local and systemic safety (AEs).	a) DHEP Plus medicated plaster, 1 plaster /day b) Placebo, 1 plaster /day c) DHEP medicated plaster, 1 plaster /day topically applied at the injured site and left in place for 12 consecutive hours a day for 10 days.	a) 65 b) 62 c) 60	Outpatients with mild-to-moderate **muscle contusions and sprains** of upper or lower limb with a superficial hematoma ≤ 140 cm^2 and spontaneous pain ≥ 40 mm (VAS), occurred <72 hours before inclusion.

Abbreviations: AE, adverse event; VAS, visual analogue scale.

Table 5 Summary of efficacy evaluations of DHEP Plus 180 mg medicated plaster versus Controls. Results are described as incremental effects in terms of pain reduction compared to a placebo plaster or DHEP medicated plaster. Clinical Overview Summary of the clinical development program of the DHEP Plus 180 mg Medicated Plaster, IBSA Farmaceutici Italia Srl, Italy internal data.

Study ID	Reference control	Therapeutic indication	VAS Δ at 'pain on movement' from baseline (DHEP Plus 180 mg medicated plaster vs. Control)
Costantino 2011[48]	Placebo plaster	Acute ankle sprain	Day 3: -10.05 mm ($p < 0.001$)
Coudreuse 2010[50]			Day 0/6h: -7.00 mm ($p < 0.001$)
Hoffmann 2012[49]		Muscle contusion of upper or lower	Day 3: -13.9 mm ($p < 0.001$)

		limbs	
Klainguti 2010[a51]		Muscle contusion or muscle strain with a superficial hematoma	Day 2: -4.5 mm (p <0.05)
Costantino 2011[48]	DHEP medicated plaster	Acute ankle sprain	Day 3: -5.43 mm (p = 0.004)
Hoffmann 2012[49]		Muscle contusion of upper or lower limbs	Day 3: -7.6 mm (p < 0.001)

[a]In this study, DHEP Plus was applied daily for a 12-hour period, while in the other studies DHEP Plus was applied for 24 hours/day; the difference in the application duration likely explains the lower analgesic effects observed in this study as compared to the other studies.
Abbreviation: VAS, visual analogue scale.

Table 6 Proportion [n / N (%)] of subjects achieving success, defined as ≥50% reduction of pain on movement as assessed by the patient on a visual analogue scale (0-100mm) compared with baseline, after 3 to 7 days of once-daily plaster application, by study and by treatment group, with relevant number needed to treat (NNT).

Study no. / ID	Assessment time point	DHEP Plus 180 mg medicated plaster	Placebo plaster	NNT (95% CI)	NNT (95% CI) at Day 7 (Studies 1 & 2 pooled)
1 / 06EU-FHP03[48]	Day 7	131/142 (92)	106/140 (76)	6.05 (4.02 – 12.21)	4.00 (3.04 – 5.83)
2 / 05DCz-FHp11[49]	Day 7	75/119 (63)	32/116 (28)	2.82 (2.11 – 4.25)	
3 / 18-12-98[50]	Day 3	51/117 (44)	37/116 (32)	8.55 (4.16 – n.c.)	

Table 7 Adverse events in phase III placebo- or active-controlled studies in the DHEP Plus medicated plaster clinical development program.

	DHEP Plus 180 mg medicated plaster (*n* = 445)	DHEP medicated plaster (*n* = 319)	Placebo (*n* = 436)
Total AEs, n (%)	24 (5.39)	26 (8.15)	36 (8.25)
Patients with AEs, n (%)	17 (3.82)	14 (4.38)	26 (5.96)
Application site AEs, n (%)	11 (2.47)	14 (4.38)	24 (5.50)
Patients with application site AEs, n (%)	8 (1.79)	8 (2.50)	18 (4.12)

Figure legends

Figure 1 Schematic representation of the medicated plaster, consisting of a polypropylene film release liner which adheres to a hydrophilic paste applied to an unwoven polyester felt backing cloth. Each plaster consists of 14 g of paste that contains 180 mg of diclofenac epolamine and 5,600 IU (approximately 28 mg) of heparin sodium in a 10 cm x 14 cm plaster. The quantity of paste spread on a plaster, 1000 mg/m^2, was designed to prevent a decrease in adhesive strength of the plaster resulting from evaporation of water during the application. The plasters are packed in a composite material envelope; in use, the patient removes the release liner and applies the self-adhesive plaster to the area being treated. Image courtesy of IBSA Institut Biochimique S.A.

Figure 2 Comparative cumulative amount of diclofenac epolamine permeation over time for the reference marketed DHEP medicated plaster and the DHEP Plus medicated plaster measured through the MatTek EpiDerm™ EPI-606-X membrane. Study DRT-18.125.275b[47].

Figure 3 Reported visual analog scale (VAS) pain reductions compared with placebo for DHEP Plus 180 mg medicated plaster and other topical nonsteroidal anti-inflammatory drugs (NSAIDs). Unless otherwise stated, data (difference vs. placebo in average score on a 100-mm VAS) are after 7 days of treatment[49,54-58].

Figure 4 Effects of pain on movement during the two-week study period in patients with mild-to-moderate contusions in the presence of hematoma and treatment with standard DHEP medicated plaster versus DHEP Plus medicated plaster versus placebo. Reproduced with permission[49].