

Nimulid™ Transgel

1. Introduction

Nimulid Transgel is a patented topical dosage form of Nimesulide. It is indicated for acute musculoskeletal disorders including sprains, strains, tendinitis, tenosynovitis, low back pain, posttraumatic inflammation and pain, peri-arthritis and osteoarthritis, morning stiffness. The transparent gel is non-sticky, non-staining and patient friendly

2. Nimulid™ Drug delivery system

Nimesulide is insoluble in most of the solvents used for the preparation of semisolid topical dosage forms. The product has been formulated using a novel combination of solvents for solubilization of Nimesulide. The solution, gelled using cellulosic and acrylic polymers, forms a thin film on the skin after application. This film acts as a reservoir facilitating better absorption of Nimesulide into the skin. Moreover, the flux created by the super-saturated solution also aids in penetration of Nimesulide into the skin.

To protect the product, it has been packed in a specially structured laminate. This laminate prevents the loss of volatile solvents upon repeated applications, thus maintaining efficacy of the formulation.

3. Clinical Experience

3.1 Pre clinical studies

- A study was conducted to evaluate the antinociception induced by a new gel formulation of Nimesulide when applied on the skin. Efficacy of topical Nimesulide gel 1% (w/w) was studied on mice in the acetic-acid-induced writhing, tail flick latency (TFL) test and formalin-induced pain models. The antinociceptive effect of Nimesulide was compared to diclofenac gel (1% w/w). Both the drugs induced dose-dependent analgesia with peak effect seen between 90 and 120 min after treatment. Greater antinociceptive effect (expressed as percent maximum possible effect) was seen in the writhing test than in the TFL test, indicating the peripheral action of both drugs. Nimesulide evidenced significant protection in the first phase

of formalin-induced pain indicating modulation of peripheral nociceptors unlike other conventional NSAIDs. This suggests that COX-2 may be a primary contributor to afferent evoked increase in prostanoid-mediated changes in pain processing. Antinociception seen following drug application on the skin was lower than that seen on intraperitoneal administration, indicating localised action following topical application. The findings of the present study suggest that the Transdermal gel formulation of Nimesulide provides significant analgesic activity when applied topically.

- ▪ In the anti-inflammatory models of formalin and carrageenan induced inflammation as well as in Freund's adjuvant induced edema models **Nimulid Transgel** showed a significant potency as compared to the equidose of diclofenac and piroxicam gels. The percent reduction in paw edema volume in carrageenan induced inflammatory model was 64% with diclofenac gel and 71.18% with **Nimulid Transgel**; in formalin induced inflammatory model, it was 12.5% with diclofenac gel and 35% with **Nimulid Transgel**. The percent reduction in paw edema volume in Freund's adjuvant induced arthritis was also highly significant with **Nimulid Transgel** as compared to diclofenac and piroxicam gel.

3.2 Toxicological studies

- ▪ Topical application of **Nimulid Transgel** in graded doses (1% and 2%) on the skin of guinea pigs daily for 14 days did not produce any signs of biological reactivity. Hematological and histological (skin) features remained unaltered in the animal studies. Thus the preparation is devoid of any adverse effect when applied chronically on the skin of guinea pigs.
- ▪ **Nimulid Transgel** was also evaluated for primary skin irritation, eye irritation and photo toxicity in rabbits. **Nimulid Transgel** does not cause allergic manifestation, reddening etc. Photo toxicity studies have shown that **Nimulid Transgel** does not cause erythema or any other allergic manifestation even on

exposure to ultra violet - A rays. Patch test applied for 72 hours in rabbits did not reveal any allergic reaction.

3.3 Clinical trials

- A double-blind comparative study was conducted in healthy human volunteers to compare the analgesic efficacy and pharmacokinetics of a new topical gel formulation of Nimesulide (10mg of pure drug) with that of placebo, diclofenac and piroxicam gels (10mg of pure drug) in three parallel groups in a double-blinded, randomized fashion with vehicle placebo.

Results

Nimesulide exhibited better efficacy than diclofenac, piroxicam and placebo. It demonstrated faster onset of action in accordance with earlier studies. Cmax is reached rapidly within 120 min of application, which correlates with the peak analgesic effect seen with Nimesulide. Significant concentration of Nimesulide could be detected in the blood within 30 minutes of treatment and persisted for 8 hours post treatment. The superior analgesic activity of Nimesulide (as a gel formulation), correlating with its pharmacokinetic profile, indicates that the topical route of administration may be a safe and effective alternative to the presently used oral and rectal routes.

- In an open labeled multi centric study involving 119 evaluable patients Nimesulide Transdermal gel (**Nimulid Transgel**) was evaluated for its efficacy and safety in painful musculoskeletal conditions

Results

A statistically significant difference was observed in the pain relief during the treatment period in all musculoskeletal conditions. There was a decrease in tenderness and analgesic intake in all conditions. In addition, there was an improvement in the daily activities. There were no side effects observed during the entire study period. The study suggests that **Nimulid Transgel** is efficacious in the treatment of painful musculoskeletal conditions.

- In a single blind, randomized, comparative evaluation of Nimesulide gel (**Nimulid Transgel**) versus diclofenac and piroxicam gel in acute musculoskeletal conditions, two hundred and seventy six patients were analyzed for assessing the efficacy and safety of these gels

Results

More number of patients got better relief in pain and inflammation parameters with Nimesulide Transdermal gel than the other two groups. The drug related side effects were low and not significant. The analysis showed that treatment with Nimesulide Transdermal gel was significantly more effective than diclofenac gel and clinically better than piroxicam gel

- A randomized double blind placebo controlled study was conducted to assess the role of commercial Nimesulide gel in the management of muscle soreness.

Time Duration	Pressure Pain Threshold		Pressure Pain Tolerance		Tenderness	
	Placebo	Nimesulide	Placebo	Nimesulide	Placebo	Nimesulide
Pre-exercise	0	22.6 ± 10.1	0	20.1 ± 10.6	0	0
Imm.-after	-5.2 ± 6.7	15.6 ± 11.5	-7.9 ± 7.6	5.5 ± 8.65	173.1 ± 74.4	57.1 ± 33.0
24 h	-24.5 ± 5.9	2.0 ± 7.7**	-19.7 ± 4.1	-3.5 ± 12.1	285.7 ± 120.2	86.8 ± 42.4
48 h	-9.6 ± 7.9	15.5 ± 10.9	-8.9 ± 6.1	17.6 ± 13.1	307.1 ± 13.1	36.9 ± 28.7*

Table 1 : Analgesic effects of Nimesulide topical application (*P < 0.05, **P < 0.01)

Results

This study showed that the subjects developed significant post-exercise muscle soreness at 24 h after performing eccentric exercise on our recently developed hand exerciser. The study also showed that commercial Nimesulide gel (**Nimulid Transgel**) application significantly relieves both the pain experienced during the performance of intense eccentric exercise and the post-exercise muscle soreness as compared to the placebo group

4. IPR Status

Product patents are filed in all major countries across the globe and patent is already granted in the following countries :

Australia, Bangladesh, Bulgaria, Canada, Japan, Kazakhstan, Myanmar, New Zealand, Nigeria, Norway, Pakistan, Philippines, Russia, South Africa, Sri Lanka, Ukraine, USA, Zimbabwe

5. Development Status

- Commercialized in the Indian market
- CTD compilation under process for regulated markets

6. Product Presentation

Nimulid Transgel™

Nimesulide Transdermal Gel

Each 30g tube contains:

Nimesulide 300mg

In a water soluble gel base

Alcohol content 66% v/v

