

Nimulid SAFEINJECT®

**WORLD'S FIRST INJECTABLE DOSAGE FORM OF
NIMESULIDE**

1. Introduction

Nimulid SAFEINJECT® developed by Panacea Biotec is the **world's first injectable dosage form of Nimesulide**. Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) indicated for the **management of a variety of painful and inflammatory conditions** like postoperative pain, primary dysmenorrhea and painful osteoarthritis. Nimesulide is currently marketed in more than 50 countries and till date, approximately 346 million treatment courses have been administered during Nimesulide's 19 years of presence in the market. With the recent concerns associated with the safety of selective COX-2 inhibitors, there has been increased interest and preference for Nimesulide due to its unique COX-1 / COX-2 selectivity ratio and established safety and efficacy.

2. Nimulid SAFEINJECT® Drug delivery system

The product has been formulated using co-solvent technique. The injection is a light yellow colored, clear, transparent liquid available at a convenient to administer dosage of 75 mg per 2 ml. The dosage strength selection of 75 mg i.m. has been determined after extensive clinical trials. Pain at the site of injection is very low due to the low viscosity of the formulation. High concentration of injection permits flexibility of dose with respect to age and condition of the patient. The formulation uses solubilization techniques to achieve high concentrations of Nimesulide and does not use any salt forms or complexation agents. The solvents used for the formulation are internationally approved for parenteral use.

3. Clinical Experience

3.1 Study I

A randomized, crossover, assessor-blind study in 13 healthy Indian volunteers was done to investigate the pharmacokinetics of Nimesulide 1mg/kg administered intramuscularly and the secondary objective was to compare the tolerability of the formulation versus placebo (vehicle only).

Observations:

- The 1mg/kg dose gave a mean C_{max} of 2.36±0.94 mg/L, and t_{max} was 2.73±1.07 h. The AUC₀₋₄₈ was 22.57±7.67 mcg.h/ml and AUC_{0-∞} was 23.96±7.59 mcg.h/ml. For the 4-hydroxy Nimesulide metabolite, C_{max} was 0.76±0.33 mg/L and t_{max} was 5.04±1.34 h.

Conclusion:

- Parenteral NSAIDs have shown good analgesic efficacy in general surgery coupled with the advantage of an opioid-sparing effect. The 1-mg/kg dose of this Nimesulide formulation can be used as the starting dose for phase II clinical studies.

3.2 Study II

A randomized, comparative, non-blinded, multicentric trial to evaluate the efficacy, safety and pharmacokinetics of 1mg/kg intramuscular Nimesulide in post – operative pain (Phase II)

Observations

- The pain reduction was significantly better with **Nimulid SAFEINJECT®** as compared to Diclofenac at 8 and 12 hrs after first dose and 0.5 and 1 hrs after the second dose. There was no significant difference in pain reduction between **Nimulid SAFEINJECT®** and Diclofenac thereafter.
- No side effects were seen in any of the patients in either group. There was no local reaction or pain seen at the injection site.

Conclusion

- **Nimulid SAFEINJECT®** when used in patients of postoperative pain has shown a good efficacy and safety.

3.3 Study III

An open label, non-comparative, multicentric study was carried out in 40 consenting patients to evaluate the efficacy and safety of intramuscular Nimesulide in post-operative pain (Phase II Extn. study)

Observations

- ▪ The pain relief was statistically and clinically significant within 30 minutes after the administration of first dose in postoperative patient. There was a 30% and 47% decrease in mean pain score as compared to baseline after 1 and 2 hrs of first dose. Thereafter, at 4 and 6 hrs, the mean pain scores and mean percentage reduction in pain scores were found to be maximum (97% and 94%) suggesting maximum effect at this point. There was a steady decrease in mean pain scores till 8 hrs and continued to show the reduction of 63% in mean pain scores at 12 hrs reporting a sustained kind of Nimesulide injection. When the second dose was given at 12 hrs, pain reduction was observed maximum at 16 to 18 hrs with sustained effect till 24 hrs. Administration of 3rd and 4th dose showed a similar trend in term of reduction in mean pain scores on VAS scale.
- ▪ No side effects were seen in any of the patients. Local tolerability at the site of injection was good. Also, no significant difference was observed in various laboratory parameters done before and after administration of Nimesulide injection.

Conclusion:

- ▪ **Nimulid SAFEINJECT®** when used in patients of postoperative pain has shown a good efficacy and safety

3.4 Study IV

A comparative, multicentric study to determine analgesic efficacy and safety of **Nimulid SAFEINJECT®** against Diclofenac injection in which 122 consenting patients were randomly assigned to receive **Nimulid SAFEINJECT®** (75 mg twice daily) or Diclofenac injection (75 mg twice daily).

Observations

- ▪ The mean pain relief was statistically and clinically significant within 30 minutes of administration of first dose and there was no significant difference in the pain intensity between **Nimulid SAFEINJECT®** and diclofenac groups at any of the time point after the first dose. Maximum analgesia was seen at 4-6 hrs in the both the groups. There was a steady decrease in mean pain score till 12 hrs reporting a sustained kind of action with the study medications. The pain relief was significantly better with Diclofenac injection at 12 hrs after the second dose. On the other hand, there was a significantly better pain relief achieved with **Nimulid SAFEINJECT®** injection at six hours after third dose and at 30 min and one hour after the fourth dose.
- ▪ 15.62% patients in Diclofenac group and 5.5% patients in **Nimulid SAFEINJECT®** group experienced mild to moderate adverse event consisting of nausea, vomiting, diarrhoea, epigastric pain, abdominal pain and pain at injection site.
- ▪ Also, no clinically and statistically significant difference was observed in various laboratory parameters done before and after administration of Nimesulide injection and Diclofenac injection.

Conclusion

- ▪ Nimesulide injection has rapid onset of action (within 30 min), high efficacy and well-sustained type of action. It also demonstrated adequate safety in the patients evaluated in this clinical trial. Therefore, **Nimulid SAFEINJECT®** injection has the potential for being an alternative parenteral analgesic in the management of postoperative pain.

3.5 Study V

A study to compare the efficacy and safety of intramuscular Nimesulide injection (75 mg Vs 100 mg) in post-operative pain in an open labeled comparative and multicentric study conducted on 53 patients meeting the inclusion and exclusion criteria.

Observations

- ▪ The mean time of onset of analgesia in **Nimulid SAFEINJECT®** 75 mg group and **Nimulid SAFEINJECT®** 100 mg group was 26.21 + 3.50 and 25.21 + 4.38 minutes respectively.
- ▪ The mean pain relief scores were statistically and clinically significant within 30 minutes of administration of first dose in both the strength and there was no significant difference in the pain intensity between two groups at any point of time after the first and second dose. Peak analgesic effect was seen at two hrs in **Nimulid SAFEINJECT®** 100 mg and four hours in **Nimulid SAFEINJECT®** injection 75 mg. There was a steady decrease in mean pain score until 12 hrs indicating a sustained action with both the study medications.

Conclusion

- ▪ Administrations of either dose (75 mg or 100 mg) of **Nimulid SAFEINJECT®** injection produced comparable efficacy in terms of onset of action, reduction in pain scores and produced sustained effect in patients of postoperative pain. Considering the response seen in terms of pain relief in either group, using higher dose (100 mg) of **Nimulid SAFEINJECT®** injection twice daily does not appears to be rational.

4. IPR Status

Product patents have been filed in all major countries across the globe and is already granted in the following countries

Australia, Bangladesh, Bulgaria, Canada, China, Europe, Ghana, Israel, Japan, Kazakhstan, Kenya, Korea, Malaysia, Mexico, Myanmar, Nepal, New Zealand, Nigeria, Norway, Philippines, Russia, South Africa, Sri Lanka, USA, Uganda, Ukraine, Yugoslavia, Zimbabwe

5. Development Stage

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

6. Product Presentation

Nimulid SAFEINJECT®

Nimesulide Injection

Each ampoule contains:

Nimesulide BP

75.0 mg

Benzyl Alcohol BP 2% v/v

(as preservative)

