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CLINICAL PRACTICE

# A single centre experience with clinical use of Neria™ Guard as mode of pain and distress management in the administration of emicizumab in children

Maj Friberg Birkedal

**Background:** The introduction of emicizumab as prophylactic subcutaneous (SC) administered treatment for people with haemophilia A has revolutionised its treatment and care; SC injection and the infrequent treatment intervals that can be achieved with emicizumab reduces treatment burden and interference in daily life. The efficacy and safety of emicizumab have been investigated in the Haven 1-7 trials. In contrast to the 4% of enrolled patients experiencing pain at the injection site across all seven trials, 11 out of 16 families at our treatment centre reported pain-related distress in administering emicizumab to their children, despite the application of local analgesia. **Aim:** The study aimed to retrospectively evaluate whether using the Neria™ Guard infusion set, a single-use medical device for SC drug delivery that allows for slow infusion, reduced pain and distress in children receiving emicizumab. **Methods:** This single-centre retrospective study included 11 paediatric patients whose families were introduced to the Neria™ Guard infusion set with the intent of reducing pain and distress. Plasma emicizumab values were tested after the introduction in relation to routine clinical check-ups in all patients. Data was collected retrospectively from patient files. According to local regulations ethical approval and consent was not necessary. **Results:** Parents/caregivers had no difficulty learning how to use the system; a single demonstration was sufficient in all cases. All

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A retrospective study finds the Neria™ Guard device to be effective in reducing pain and distress among children receiving treatment with emicizumab but recognises the need for further research and a validated, stability-tested solution

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**families reported a reduction or complete resolution of pain and distress in relation to emicizumab injection after the introduction of Neria™ Guard, and all families have continued using the device. Plasma levels of emicizumab were sustained within the target therapeutic range. Conclusion: There is a need for more recognition of and research into the prevalence of pain and distress among children receiving treatment with emicizumab, and a need for a validated and stability tested solution to alleviate this. Neria™ Guard has proven to be effective in the reduction of pain and distress in our clinic.**

**Keywords:** *Children, Emicizumab, Haemophilia, Pain management, Patient experience, Distress*

The introduction of emicizumab as prophylactic treatment for people with haemophilia A, delivered subcutaneously (SC), has revolutionised treatment and care for this patient group. Previously, prophylactic treatment could only be administered by frequent intravenous (IV) injections. By contrast, SC injection is a simpler technique and requires less dexterity. The longer treatment intervals that can be achieved with emicizumab have been shown to reduce treatment burden and interference in daily life [1,2,3,4]. The efficacy and safety of emicizumab have been investigated in the Haven 1-7 trials [5,6,7,8,9,10,11]. However, at our treatment centre we experienced discrepancies between the Haven trials' reported occurrence of pain, both in the clinical experiences of nurses and the reported lived experience of the families administering emicizumab to their children.

The Haven 1-7 trials found injection site reactions (ISRs) in 15-30% of all enrolled patients. The most reported ISRs were injection site rash (11%), injection site itching (3%), and injection site pain in 4% of enrolled patients across all seven trails [5-11]. Despite this low reported incidence of pain, we experienced a high incidence of families reporting distress in relation to injections. Parents reported a need for one parent to forcefully restrain their child while a co-parent gave the injection. The treatment team was often not informed of the gravity of the situation until it had become emotionally unbearable for all parties involved or the child had become too large/strong to restrain.

We began systematically interviewing all our families during routine visits, encouraging them to narrate the entire process of emicizumab administration, from the days leading up to the injection to the days after. Of 16 families treating their children with emicizumab, 11 reported distress in relation to administering the treatment. Parents reported children hiding under tables and beds to avoid the injection, a stressful and tense atmosphere on the day of injection, sleep interference in the days leading up to the injection, kicking, screaming, spitting, crying during the injection, and the need for physical restraint to complete the injection. Overall, the families cited pain as the primary cause of the distress.

Searching for a way to reduce pain, distress, and the use of physical restraint, the care team suggested introducing Neria™ Guard for the delivery of emicizumab. Neria™ Guard is a medical device designed for SC drug delivery. By pushing a button, a fully automatic insertion of a soft catheter attached to a cannula housing is delivered in the subcutaneous tissue. Once the catheter and housing are delivered, a prefilled line is connected to the housing, allowing for slow infusion of drugs.

Neria™ Guard is often used for the delivery of iron chelation therapy (deferoxaminmesilat) for thalassemia patients, and has undergone stability testing for immunoglobulins, morphine and apomorphine [12]. However, the device, which contains various plastic components, has not been stability tested for emicizumab. The interaction between medical plastics and drugs is complex and there are several known examples of biological substances that adhere and interact with plastic, such as insulin and heparin [13]. Drug absorption into plastics may affect drug dosage, and the migration of plastic additives into a drug solution may affect drug composition and, ultimately, its efficacy [14]. Emicizumab has been found to have no incompatibilities with polypropylene and polycarbonate [14]; however, Neria™ Guard contains plastics that are a subcategory of polycarbonate but have other compositions of polymeric chains. To date, there have been no studies directly testing compatibility between Neria™ Guard and emicizumab. However, we found no cause for major safety concerns.

**Figure 1. Photographs showing use of the Neria™ Guard device, which enables slow infusion during subcutaneous drug delivery**

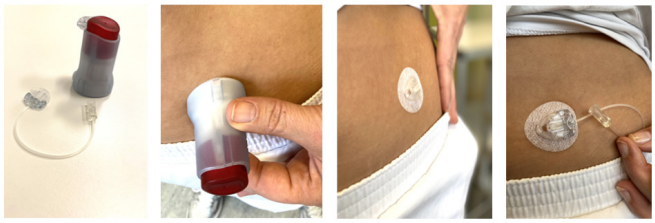
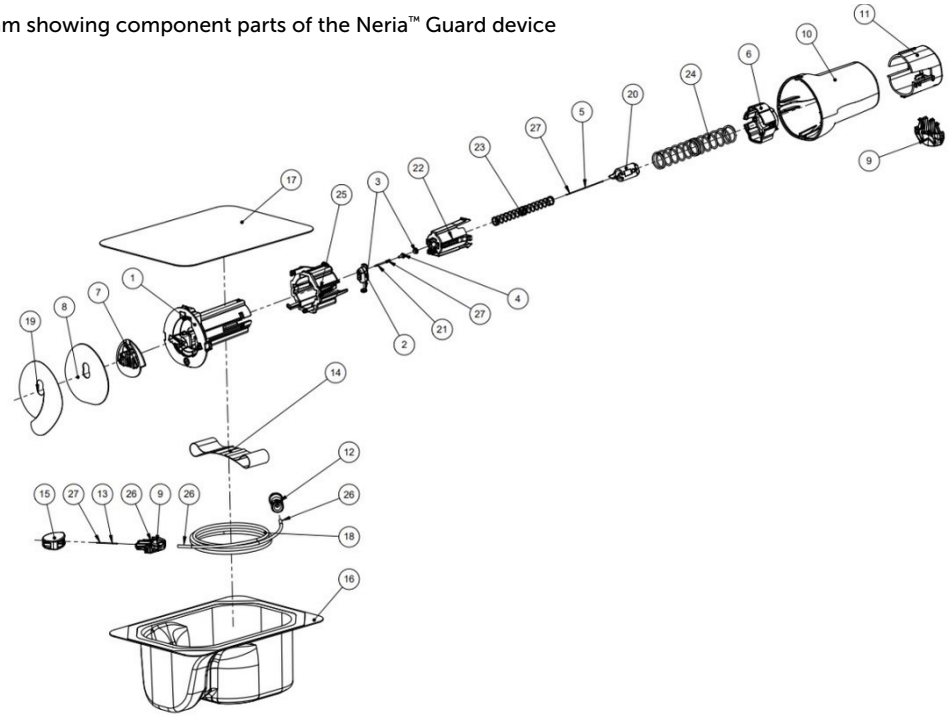


Figure 2. Diagram showing component parts of the Neria™ Guard device



| COMPONENT NUMBER | COMPONENT | MATERIAL |
|---|---|---|
| 1 | Cylinder | Polypropylene (PP) |
| 2 | Fluid part base | Polypropylene (PP) |
| 3 | Septum (injection port) | Silicone, Elastosil |
| 4 | Bushing | Polycarbonate (PC) |
| 5 | Introducer needle | Stainless steel, AiSi 304 |
| 6 | Releaser | Polyoxymethylene copolymer (POM) |
| 7 | Base | Co-polyester |
| 8 | Adhesive patch | Polyester with polyacrylate adhesive |
| 9 | Connector in grey colour | Methyl methacrylate acrylonitrile butadiene styrene (MABS), Terlux 2802 HD, transparent, grey |
| 10 | Cover | Polypropylene (PP), grey |
| 11 | Release button | Polypropylene (PP), red |
| 12 | Luer | Methyl methacrylate acrylonitrile butadiene styrene (MABS), Terlux 2802 HD, transparent |
| 13 | Connector needle | Stainless steel, AiSi 304 |
| 14 | Fixation tape | Bandarole, Flexpeel |
| 15 | Protective cap for connector | Polypropylene (PP) |
| 16 | Blister | Amorphous polyethylene terephthalate/polyethylene (APET/PE) |
| 17 | Blister lid | Medical grade paper |
| 18 | Extruder tube:<br>Inner tube<br>Outer tube | <br>Polyethylene (PE)<br>Polyurethane (PUR) |
| 19 | Reinforcement liner<br>(part of adhesive patch ID #8) | Polyethylene terephthalate (PET) and acrylic adhesive |
| 20 | Neeedle hub | Polyoxymethylene (POM) |
| 21 | Soft catheter | Polytetrafluoroethylene (PTFE) |
| 22 | Piston | Polyoxymethylene copolymer (POM) |
| 23 | Retraction spring | Stainless steel spring wire (AiSi 302) |
| 24 | Insertion spring | Stainless steel spring wire (AiSi 302) |
| 25 | Base lock | Polypropylene (PP) |
| 26 | N/A | UV glue |
| 27 | N/A | Silicone oil |

Table 1. Serum emicizumab in the study population after initiation of Neria™ Guard

| PATIENT NO. | TREATMENT INTERVAL | DAYS FROM LAST INJECTION TO BLOOD SAMPLE | DAYS FROM INITIATION OF NERIA™ GUARD TO BLOOD SAMPLE | MEASURED EMICIZUMAB PLASMA LEVELS |
|---|---|---|---|---|
| 1 | Every 14 days | 8 | 36 | 53 µg/L |
| 2 | Every 14 days | 2 | 92 | 62 µg/L |
| 3 | Every 14 days | 8 | 54 | 33 µg/L |
| 4 | 1 x week | 5 | 61 | 71 µg/L |
| 5 | 1 x week | 5 | 61 | 41 µg/L |
| 6 | Every 20 days | No data available | 56 | 52 µg/L |
| 7 | Every 14 days | 1 | 57 | 57 µg/L |
| 8 | Every 14 days | 12 | 72 | 65 µg/L |
| 9 | Every 14 days | 12 | 72 | 62 µg/L |
| 10 | Every 14 days | 9 | 37 | 48 µg/L |
| 11 | 1 x week | 0 | 35 | 49 µg/L |

This paper reports on a single-centre retrospective study aimed at evaluating whether using Neria™ Guard reduced pain and distress in children receiving emicizumab while continuing to deliver plasma levels of emicizumab within the target therapeutic range.

## METHODS

All 11 families experiencing distress in relation to the injections were offered Neria™ Guard. They were informed of the lack of safety testing with emicizumab and that we were balancing the need for an intervention against the lack of safety data. The practical application of Neria™ Guard was initially demonstrated on a dummy and subsequently the parent/caregivers applied and used the device on their child. The children were encouraged to push the ejection button themselves, providing them with the opportunity to gain control of the timing. The children were also encouraged to either administer the drug, pushing the plunger at a comfortable pace, or vocalise when they needed a reduction in speed or a break. All children using the device had local anaesthetics applied before treatment.

Serum emicizumab values were not tested per any specific timing but assessed after the introduction in relation to routine clinical check-ups. Emizicumab was measured on an automated ACL TOP 550 (IL Werfen). Calibrators were from r2 Diagnostics (Haemochrom Diagnostica) and reagents for the clotting reaction were provided by IL Werfen (HemosIL®SynthASil (APTT) and HemosIL®Factor VIII deficient plasma). The working range of the method was determined to 5-150 mg/L. Lab results data was collected retrospectively from patient files.

According to local regulations, ethical approval was not necessary.

## RESULTS

Data from patient files showed that parents/caregivers did not experience any issues in learning how to use the device. In all instances, a single demonstration sufficed. The families reported a significant reduction in pain and distress. A note on one patient file included the quote: "It's been like winning the lottery."

Most noteworthy, parents testified to an improved collaboration with their child, reporting that it was no longer a matter of coercion but teamwork focused on safeguarding the child's integrity. All 11 families experienced reduced stress in follow-up visits. All families, other than those with the youngest patients (aged 0-2 years; n=4) discontinued the use of physical restraint. All families have continued using the device.

All patients have sustained plasma levels of emicizumab within the targeted therapeutic range, between 30-80 micrograms/ml [15,16] (see Table 1).

## DISCUSSION

Through the Haven trials, it can be established that pain and distress in children treated with emicizumab is not uncommon [5-11]; however, there is a general lack of evidence regarding its prevalence in its routine use. In a survey sent out via the European Association for Haemophilia and Allied Disorders (EAHAD) nurses' network in 2023, nurses from ten European countries reported an increase in distress and use of restraint in children receiving emicizumab compared with children on IV treatment [17]. It was estimated that up to 60% of

all children experienced pain in relation to the injection of emicizumab. The survey respondents identified the volume of the injected medicine, how rapidly it was administered, and the use of restraint to be the three major contributors to pain and distress. Mitigation strategies included the application of local anaesthesia, distraction, sugar solutions for infants, nitrous oxide, sensory stimulation with the use of shot blockers, ice, pinching, and use of the Buzzy bee® device. The World Federation of Hemophilia (WFH) guidelines for the management of haemophilia do not address pain in relation to SC injections in their recommendations for pain management [18].

Pain and distress in children receiving emicizumab has become a noticeable problem in our centre and others but seems to be an issue often avoided in discussions with parents. Families who now treat their children with emicizumab that used to struggle with inhibitors, poor venous access and infections related to central venous access devises (CVADs) are arguably more reluctant to complain about pain and distress, as for them this is not a potentially life-threatening complication. The reduction in overall treatment burden may mean that acceptance of pain and distress is perhaps considered a prerequisite if their child needs access to SC treatment.

The prevalence of pain and distress in children related to emicizumab injections is yet to be investigated independently from pharmaceutical companies. In a 2023 study conducted by the Netherlands Haemophilia Society, members were asked to report if they experienced pain in relation to injection of emicizumab; distress was not included in the study [19]. The survey had 72 respondents; 72% (n=52) reported pain, half of whom reported that the pain was problematic. This method of a voluntary survey in a patient organisation is naturally biased towards persons experiencing pain. However, with a total of 209 people treated with emicizumab in The Netherlands at the time the survey was conducted, and with 52 members experiencing pain during injection, this survey suggests that the number of people experiencing pain issues during injection is at least 25%, most of whom are children [20].

The discomfort of administrating emicizumab is related to the volume delivered and the speed of administration; the faster you administer the drug, the more painful it becomes, though slow or staggered infusion reportedly reduces this [20]. Under these circumstances, it is a natural response for the child to try to resist treatment. The child's resistance often causes the caregiver to apply physical restraint and administer the infusion even faster to ensure completion, with a compounding effect on the perceived pain and distress. The use of physical restraint is often taboo and considered stigmatizing and shameful [20]. Subsequently, it can be difficult to admit and disclose its use even with a trusted treatment team.

Physical restraint is associated with both short-term consequences, such as reduced ability to form trustful relationships and delayed development of speech, and long-term consequences. In up to 25% of all adults that have needle phobia, the cause is rooted in childhood experiences that can lead to avoidance of healthcare services later in life [21].

Moreover, children's maladjustments to their illness are associated with high levels of distress in parents. Using self-reported screening tools like the distress thermometer for parents of a chronically ill child (DT-P) could effectively capture the distress experienced by these families [17] and serve as a starting point for the coordination of care.

In our study, the used of Neria™ Guard showed positive results; however, there is an unmet need for a validated and stability tested solution to alleviate distress in children receiving emicizumab. F. Hoffmann-La Roche and Convatec, the manufacturer of Neria™ Guard, have been approached for potential collaboration on safety testing related to the introduction of Neria™ Guard. Unfortunately, such a collaboration has not been possible to initiate, and the need for a collaborative effort exploring innovative approaches remains. At the time of writing, emicizumab was the only licensed SC haemophilia treatment available in Denmark, but one can speculate that the pain and distress associated with its administration may be similar with the introduction of other SC treatments in the future.

To improve patient care, standardised protocols should be developed to establish consensus on the optimal timing of evaluation of plasma levels, taking emicizumab's long half-life into consideration. Such a consensus might be further complicated by the increased use of personal tailoring of emicizumab treatment with whole vial prescriptions [22].

## CONCLUSION

Caregivers of children receiving emicizumab at our treatment centre struggle with a complex paradox: protecting and caring for their child, versus a willingness to do anything to ensure their treatment despite the pain and distress associated with it, including the practice of forceful restraint [21]. Due

to the stigma associated with forceful restraint, families potentially struggle in silence. Implementing a coordinated and systematic interview routine for all families treating their child with emicizumab could help uncover the specific routines families follow, potentially revealing unrecognized distress among children receiving emicizumab.

There is a need for more recognition of and research into the prevalence of pain and distress among children receiving treatment with emicizumab, and a need for a validated and stability tested solution to alleviate this. Our small retrospective study supports the effectiveness of Neria™ Guard in reducing the pain and distress associated with treatment, and it will continue to be a valuable method of emicizumab delivery at our clinic. Although there is no safety data available to validate the safe use of Neria™ Guard and emicizumab, all patients involved in the study remained within therapeutic range of emicizumab after initiation. This is not a concrete proof of compatibility but has served as a helpful guide at our clinic.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## Consent

Informed consent has been obtained from the parents and caregivers in the retrospective study reported in this paper.

## Conflict of interest

The author has advised no interests that might be perceived as posing a conflict or bias.


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