QT PROLONGATION WITH MACRILEN™ (MACIMORELIN)

Prescribing Information

The concomitant use of Macrilen™ with drugs that are known to prolong the QT interval should be avoided. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases.[1]

Per the Macrilen™ Prescribing Information, a single dose of Macrilen™ (2 mg/kg) resulted in a mean baseline- and placebo-adjusted change (upper single-sided 95% confidence interval) in the QT interval corrected for heart rate according to Fridericia (QTcF) of 9.6 milliseconds (msec) (11.4 msec) at 4 hours post-dose, which occurred after the mean maximum Macrilen™ plasma concentration (0.5 hours).[1]

Klaus et al. identified the 2 mg/kg as an appropriate supratherapeutic dose for use in the above mentioned Thorough QT study by Lissy et al.[2]

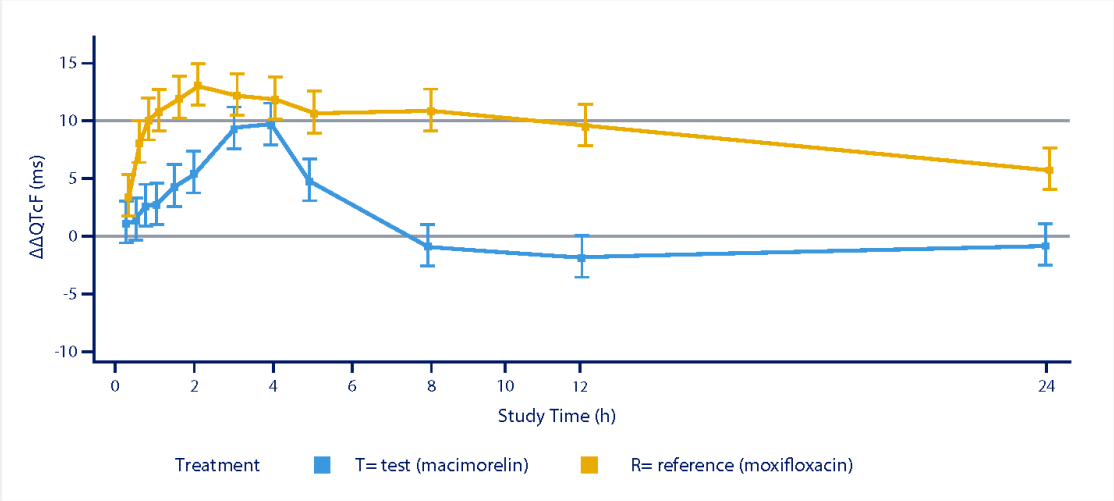
Furthermore, Lissy et al. reported that the effect on QTcF by Macrilen™ was numerically lower and shorter in duration compared to the effect exerted by moxifloxacin. Data analyses were performed in accordance with the International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use (ICH E14).[3]

The effects of both Macrilen™ and moxifloxacin on QTcF intervals can been seen in **Figure 1** below. There were no clinically relevant findings with Macrilen™ based on the interpretation of ECGs by the cardiologist.[3]

All treatment emergent adverse events (TEAEs) were of mild or moderate intensity, and resolved. Cardiovascular emergent adverse events are summarized in **Table 1** below.[3]

The Prescribing Information for Macrilen™ does not provide a recommendation on baseline ECG prior to administering Macrilen™. Novo Nordisk is unable to provide patient-specific treatment or monitoring recommendations. Decisions about the prescribing of Novo Nordisk products should be made based on your clinical judgment and an assessment of the benefits versus risks of the therapy in the specific patient.

Figure 1. Mean Placebo-corrected Changes in QTcF[a] for Macrilen™ and Moxifloxacin[3]



Lissy et al.
a. QTcF, heart rate–corrected QT interval using Fridericia's formula

Medical Information Response

QT Prolongation with Macrilen™ (macimorelin)

Summary

- The concomitant use of Macrilen™ with drugs that are known to prolong the QT interval should be avoided. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases.[1]
- Per the Macrilen™ Prescribing Information, a single dose of Macrilen™ (2 mg/kg) resulted in a mean baseline- and placebo-adjusted change (upper single-sided 95% confidence interval) in the QT interval corrected for heart rate according to Fridericia (QTcF) of 9.6 milliseconds (msec) (11.4 msec) at 4 hours post-dose, which occurred after the mean maximum Macrilen™ plasma concentration (0.5 hours).[1]
    - Klaus et al. identified the 2 mg/kg as an appropriate supratherapeutic dose for use in the above mentioned Thorough QT study by Lissy et al.[2]
    - Furthermore, Lissy et al. reported that the effect on QTcF by Macrilen™ was numerically lower and shorter in duration compared to the effect exerted by moxifloxacin. Data analyses were performed in accordance with the International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use (ICH E14).[3]
        - The effects of both Macrilen™ and moxifloxacin on QTcF intervals can been seen in **Figure 1** below. There were no clinically relevant findings with Macrilen™ based on the interpretation of ECGs by the cardiologist.[3]
        - All treatment emergent adverse events (TEAEs) were of mild or moderate intensity, and resolved. Cardiovascular emergent adverse events are summarized in **Table 1** below.[3]
- The Prescribing Information for Macrilen™ does not provide a recommendation on baseline ECG prior to administering Macrilen™. Novo Nordisk is unable to provide patient-specific treatment or monitoring recommendations. Decisions about the prescribing of Novo Nordisk products should be made based on your clinical judgment and an assessment of the benefits versus risks of the therapy in the specific patient.

Prescribing Information[1]

Section 5.1: Warning and Precautions, QT Prolongation

Macrilen™ causes an increase of about 11 msec in the corrected QT (QTc) interval. QT prolongation can lead to development of torsade de pointes-type ventricular tachycardia with the risk increasing as the degree of prolongation increases. The concomitant use of Macrilen™ with drugs that are known to prolong the QT interval should be avoided.

Section 7.1: Drug Interactions, Drugs that Prolong QT Interval

Co-administration of Macrilen™ with drugs that prolong the QT interval (such as antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QT interval) may lead to development of torsade de pointes-type ventricular tachycardia. Avoid concomitant use of Macrilen™ with drugs that prolong the QT interval.

Sufficient washout time of drugs that are known to prolong the QT interval prior to administration of Macrilen™ is recommended.

QT Interval Correction

The QT interval in an electrocardiogram (ECG) is a measurement of the duration of ventricular depolarization and repolarization.[4] Prolongation of the QT interval may lead to an increased risk of cardiac arrythmias, torsade de pointes, ventricular fibrillation, possibly leading to cardiac death. For the purposes of accurately interpreting the QT interval, rate correction (QTc) is utilized to compare the measurements at different time points and heart rates.[5]

As the primary variable for the evaluation of Macrilen™ effects on the ventricular de- and repolarization duration, the QT interval corrected for heart rate according to Fridericia (QTcF) was chosen for both phase 1 studies, Lissy et al. and Klaus et al. A scatter plot of mean QT versus mean RR showed that the use of the heart rate correction according to Fridericia (QTcF) was appropriate for this study.[3] A study looking to determine the accuracy of different correction formulas in an automated QT-monitoring algorithm in an electronic medical record found the Fridericia formula resulted in one of the more accurate rate corrections and significantly improved prediction of 30-day and 1-year mortality.[5] The Fridericia QT correction for heart rate is performed using the following formula: $QTcF=QT/RR^{1/3}$.[5]

Section 12.2: Clinical Pharmacology, Pharmacodynamics: Cardiac Electrophysiology[1]
The effects of Macrilen™ on ECG parameters were investigated in a dedicated QT study that investigated, in a 3-way cross-over design with 60 healthy subjects, the effects of a supra-therapeutic dose of Macrilen™ (2 mg/kg) (4 times the recommended dosage) in comparison with placebo and with moxifloxacin. This study showed a mean baseline- and placebo-adjusted change (upper single-sided 95% confidence interval) in QTcF of 9.6 msec (11.4 msec) at 4 hours post-dose, which occurred after the mean maximum Macrilen™ plasma concentration (0.5 hours). A similar increase in the QTcF interval was also observed in a single-ascending dose study, which included three dose levels (0.5 mg/kg, and 1 mg/kg and 2 mg/kg [2 times and 4 times the recommended dosage, respectively]). All three dose levels studied showed a similar magnitude of QTcF prolongation in the Thorough QT study, suggesting an absence of dose dependent changes. The mechanism for the observed QTcF prolongation is unknown.

The single-ascending dose study by Klaus et al. and the Thorough QT study by Lissy et al. are discussed further in detail below.

Klaus et al. (Single-Ascending Dose Study)
In this phase 1 study, which evaluated three single-ascending doses of Macrilen™ in healthy adults, the mean QTcF intervals were prolonged by approximately 10 to 11 msec for all 3 Macrilen™ dose groups at 3 to 4 hours post-dose based on a triplicate 12-lead ECG. For subjects that received Macrilen™, other cardiac safety parameters assessed using standard 12-lead ECGs were not significantly affected. At 8 hours post-dose, all dose groups, including placebo, showed a mean shortening of the QTcF interval of 10 to 13 msec. This study identified the 2 mg/kg as an appropriate supratherapeutic dose for use in the Thorough QT study.[2]

Lissy et al. (Thorough QT Study)

The Thorough QT study investigated the effect of Macrilen™ 2 mg/kg on ECG safety variables, in particular on cardiac depolarization and repolarization duration. Of the 60 healthy adult subjects, 56 completed all three treatment periods, and cardiac safety data was collected from 59 subjects. All subjects had to have a normal ECG recording based on 12-lead ECG or recordings with slight deviations that were deemed by the investigator as not clinically relevant. Subjects with a family history of long QT syndrome or torsade de pointe were excluded. Data analyses were performed in accordance with ICH E14.

Each subject received a single oral dose of Macrilen™ 2 mg/kg (blinded), matching placebo (blinded), or moxifloxacin 400 mg tablet (open-label) in a randomized order over the course of three periods with at least 3 days of washout period between administrations. All subjects returned to study center on day 1 of each period, and discharged after 24 hours post-dose period. All drugs were administered with 240 mL of water after 8 hours of fasting, with the exception of water.[3]

ECGs were recorded using digital 12-lead Holter recorders continuously on the respective days of dosing at predefined timepoints before dosing and lasting for at least 24 hours after dosing. This study reported that Macrilen™ (2 mg/kg) prolonged cardiac repolarization, but the effect on QTcF by Macrilen™ was numerically lower and shorter in duration compared to the effect exerted by moxifloxacin. The effects of both Macrilen™ and moxifloxacin on QTcF intervals can be seen in **Figure 1** below. At all time points, Macrilen™ induced mean placebo-corrected prolongation of QTcF was smaller at all time points, and had a smoother rise with a sharper decrease until about 6 hours after dosing compared to moxifloxacin. The maximum observed QTcF change during Macrilen™ treatment for an individual subject was 38 msec. No effects on other ECG parameters were noted by the cardiologist, and there were no clinically relevant findings. After accounting for a time delay of up to about 3.5 hours between peak pharmacokinetic and peak pharmacodynamic effect, the estimated predicted mean QTcF prolongation at the maximum plasma concentration was approximately 11 msec based on this exposure-response analysis.[3]

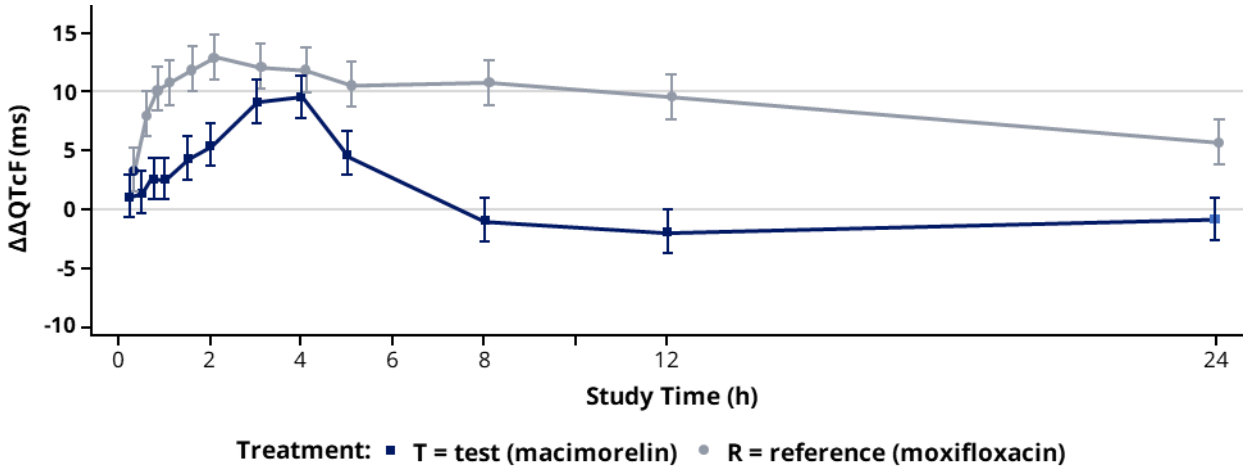


Figure 1. Mean Placebo-corrected Changes in QTcF[a] for Macrilen™ and moxifloxacin[3]

Lissy et al.

a. QTcF, heart rate–corrected QT interval using Fridericia's formula

Out of 57 subjects that received Macrilen™, 16 subjects (28.1%) reported 20 TEAEs after administration of Macrilen™,19 subjects (32.8%) reported 29 TEAEs after moxifloxacin and 5 subjects (8.8%) reported 6 TEAEs after placebo dosing. Of the 20 TEAEs reported after administration of Macrilen™, 14 TEAEs reported by 12 subjects were considered to be drug related by the investigator. The most frequently reported TEAE across treatment groups was headache, which was experienced by 8 subjects (14%) after Macrilen™ administration. There were 2 subjects who discontinued treatment; 1 subject discontinued as a result of prolonged QTcF observed 6 days after administration of Macrilen™. This was not considered to be drug-related. All TEAEs were of mild or moderate intensity. All TEAEs resolved. Cardiovascular emergent adverse events are summarized in **Table 1** below.[3]

Table 1. Cardiovascular Treatment-Emergent Adverse Events[3]

Cardiovascular Treatment-Emergent Adverse Events	**Macrilen™ 2 mg/kg N=57 n (%) e**	**Moxifloxacin 400 mg N=58 n (%) e**	**Placebo N=57 n (%) e**
ECG QT prolongation	2 (3.5) 2[a]	6 (10.3) 6	0
Sinus bradycardia	1 (1.8) 1	1 (1.7) 1	1 (1.8) 1
Systolic blood pressure increase	0	1 (1.7) 1	0
Palpitations	0	1 (1.7) 1	0

a. Includes 1 event considered unlikely related to treatment.
n (%) e: n=number of participants having the event, (%)=proportion of exposed participants having the event, e=number of events (all treatment-emergent events considered.

Baseline ECG Prior to Administering Macrilen™

The Prescribing Information for Macrilen™ does not provide a recommendation on baseline ECG prior to administering Macrilen™. Novo Nordisk is unable to provide patient-specific treatment or monitoring recommendations. Decisions about the prescribing of Novo Nordisk products should be made based on your clinical judgment and an assessment of the benefits versus risks of the therapy in the specific patient.

If you would like to receive a copy of any of the published references cited in the response, please contact Novo Nordisk Medical Information at (800) 727-6500 or NNMedicalInformation@novonordisk.com.

References

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