The PK Profile of SABER®-Bupivacaine in Humans Across Surgical Models Demonstrates Sustained 72-Hour Drug Delivery

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INTRODUCTION

• Local anesthetics, such as bupivacaine, an amide-type anesthetic that blocks the generation and conduction of nerve impulses, mitigates serious acute pain after surgery and limit the reliance on opioids; however, they provide only short periods of pain relief.

• There is an unmet need for an extended-release formulation of bupivacaine that provides reliable post-surgical pain relief during the first 72 hours.

• SABER-Bupivacaine was developed to meet this need and contains 132 mg bupivacaine base/mL (60 mg in a 5-mL dose).

• SABER-Bupivacaine is a sustained-release formulation of bupivacaine base (12%) in a controlled-release matrix composed of a fully esterified sugar derivative, guargum hydrogel (SAIB), and benzyl alcohol, administered together as a solution (Figure 1).

METHODS

STUDY DESIGN AND TREATMENT

• Eleven clinical trials have evaluated the clinical pharmacokinetics of SABER-Bupivacaine.

• Two trials in healthy subjects (subcutaneous administration).

• Nine trials in patient populations undergoing various surgical procedures (such as inguinal hernia repair, hysterectomy, laparotomy, laparoscopically assisted colectomy, appendectomy, and shoulder repair).

• In each clinical study, following baseline blood sample collection, additional PK samples were collected at specified time points until 72 hours after dosing with SABER-Bupivacaine.

• These samples were analyzed for determination of bupivacaine concentration using a validated liquid chromatography/tandem mass spectrometry method.

RESULTS

ABSORPTION/AVAILABILITY

• Absorption of bupivacaine in all surgical models was rapid, measurable drug concentrations were observed at the first evaluated time points (0.5 or 1 hour), followed by a gradual increase in concentration in all evaluated surgical models, demonstrating lack of dose dumping with the formulation1 (Figure 2).

• Across abdominal surgery types, the mean maximum plasma concentration (Cmax) varied from 625 to 989 ng/mL, and time to maximum observed plasma concentration (Tmax) ranged from 24 to 48 hours.

• Differences could be attributed to interpatient variability, surgery type, and variation in localized blood flow at the site of administration1 (Table 1).

• In shoulder surgery, the mean maximum plasma concentration (Cmax) was 731 ng/mL, and the time to maximum observed plasma concentration (Tmax) was 8 hours.

• Overall mean plasma concentrations are sustained between 400 to 600 ng/mL from 12 to 72 hours postoperatively following administration of SABER-Bupivacaine.

Table 1. Pharmacokinetic Parameters of Bupivacaine After Administration of 5 mL SABER-Bupivacaine Across Surgical Types

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hernia</th>
<th>Appendectomy</th>
<th>Lap. cholecystectomy</th>
<th>Lap. Ass. colec.</th>
<th>Laceration</th>
<th>Shoulder Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax, h</td>
<td>24</td>
<td>24</td>
<td>26</td>
<td>48</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>762</td>
<td>989</td>
<td>625</td>
<td>956</td>
<td>752</td>
<td>850</td>
</tr>
<tr>
<td>AUC(0-24 h), ng·h/mL</td>
<td>25,888</td>
<td>61,016</td>
<td>35,230</td>
<td>41,942</td>
<td>30,950</td>
<td>39,052</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• This pharmacokinetic analysis demonstrates that SABER-Bupivacaine provides immediate and continuous 72-hour delivery of bupivacaine in a variety of surgical models from a variety of incision/site administrations.

• Complete delivery of the drug was observed with SABER-Bupivacaineadministration.

• Absorption of bupivacaine after SABER-Bupivacaine administration in all surgical models was rapid and demonstrated a lack of dose dumping.

• Overall mean bupivacaine concentration was between 400 to 600 ng/mL for an extended duration from 12 to 72 hours.

• Differences in local blood perfusion, type of tissue, and patient-to-patient variability can impact pharmacokinetics.

• SABER-Bupivacaine administration was well tolerated.

SAFETY

• There were no reported treatment-related instances of serious central nervous system or cardiac adverse events traditionally associated with bupivacaine toxicity.

• No treatment-related changes in heart rate, conduction, or repolarization or treatment-emergent ventricular arrhythmias were detected by Holter monitoring.

REFERENCE


Financial Disclosures

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