Intramuscular (IM) injection is one of many routes for administering medications, including antibiotics, vaccines, hormonal therapies, and corticosteroids. Even when alternate routes of administration are available, IM injections may be preferred when a patient cannot tolerate oral medication or when adherence is a concern. IM injections also may be beneficial for absorption compared with other routes of administration (ie, faster than subcutaneous injection and slower than intravenous administration). In addition, some medications contain components that can irritate subcutaneous tissue but not muscle tissue, which also can tolerate larger fluid volumes with minimal discomfort.

Large-volume injections (3 mL or greater), however, are not frequently administered; and many clinicians may not be familiar with their appropriate use, possible side effects, and potential efficacy. Medications administered via large-volume IM injections include ceftazidime (Fortaz, Tazicef, generics), cefuroxime (Ceftin, Zinacef, generics), ertapenem (Invanz), penicillin G benzathine (Bicillin L-A, Permapen), and fulvestrant (Faslodex). This article discusses the practical issues related to administration of large-volume IM injections, in the setting of administering fulvestrant for the treatment of breast cancer, with a focus on best practices for efficacy and safety.

IM injections are administered in five potential sites: deltoid (commonly used for adult vaccinations), dorsogluteal, ventrogluteal, rectus

FIGURE 1A. Potential sites for intramuscular injection: Dorsogluteal site
femoris, and vastus lateralis\(^3,10,11\) (Figure 1). Maximum volumes have been proposed across the various IM sites for adult patients\(^3,12-16\) (Table 1). Overall, 5 mL has been cited for adults as the maximum volume for a single IM injection, with lower maximums proposed for adult patients with less-developed or small muscle mass.\(^3,13,14\)

**INTRAMUSCULAR INJECTIONS**

Once administered exclusively by physicians, IM injections became a primary-nurse responsibility during the 1960s.\(^1\) However, few evidence-based guidelines for IM injections are available, and discrepancies within nursing textbooks have been noted.\(^10-13\) In addition, current guidelines do not address administration of large-volume injections.

The dorsogluteal site for IM injections is the one nurses have the most experience using, as this is what is traditionally taught in nursing schools and covered in nursing textbooks.\(^16-18\) A recent study found that acute care nurses in Canada preferentially selected the dorsogluteal IM injection site over the ventrogluteal IM injection site.\(^19\) The majority of respondents cited their own level of comfort as the predominant reason for this preference. However, nurses who were older than 30 years, were diploma prepared, and had more than 4 years of nursing experience were more likely to choose the dorsogluteal site; whereas nurses who were age 20 to 24 years, were degree prepared, and had 1 to 4 years of nursing experience were more like to choose the ventrogluteal site.\(^19\) This finding supports the idea that the ventrogluteal site may be used more often by those who received specific guidance in administering at that site.

The ventrogluteal region (targeting the gluteus medius\(^1,16\)) and the vastus lateralis region are free of major nerves and blood vessels.\(^3,17,18\) The safety of the ventrogluteal region as an area for administering IM injections is established and the area is identified as a preferred site within clinical practice guidelines.\(^1,3,12,16-18,20\) Nevertheless, nurses are reluctant to use this site, possibly because of a lack of confidence in identifying the area or the absence of recommendations by nursing authors or within nursing education.\(^17,18,20,21\) The ventrogluteal site is identifiable by a prominent and easily palpable bony landmark; however, it is a small area, which may be an issue in the setting of repeated injections.\(^17,18\)

Inexperience with injection techniques and inaccurate landmarking can result in injection-site pain or injury.\(^16,22\) Sciatic nerve pain can occur, though rarely, if a dorsogluteal injection is given too low.\(^20,23-25\) This risk can be attenuated by selecting the upper and outer quadrant of the buttock.\(^3,10\) Both the sciatic nerve and the superior gluteal artery are only a few centimeters from this site so care should be taken to landmark the injection accurately.\(^22\) Other injection-related side effects are granuloma; intravascular injection; muscle fibrosis and contracture; tissue necrosis; hematoma; abscess; cellulitis; and injury to blood vessels, bone, and peripheral nerves.\(^3,18\)

In a small study conducted by Boyd and colleagues at MD Anderson Cancer Center in Houston, Texas, 146 of 251 intended gluteal IM injections (58%) administered by...
nurses were deemed successful by pelvic CT scan, while 105 (42%) were associated with subcutaneous nodules, indicating subcutaneous placement. Successful IM injection was associated with self-reported indicators of nursing experience, injection-site location method, depth of needle insertion, and use of nonsyringe hand. Common reasons for unsuccessful IM injection included poor injection-site selection and not advancing the needle to full length. It was estimated that needles 38 mm (1.5 inches) or more would be needed for successful IM injection in 14% to 34% of patients.26

IN THE SETTING OF HR+ METASTATIC BREAST CANCER
Fulvestrant, an estrogen receptor antagonist, is indicated for the treatment of hormone receptor-positive (HR+) metastatic breast cancer in postmenopausal women who have failed antiestrogen therapy.9 It is administered as a once-monthly IM injection with a 21-gauge, 1.5 inch (40 mm) needle. Oral therapies (eg, tamoxifen [Soltamox, generics] and aromatase inhibitors) are also routinely used for this indication.

A 2006 survey of patients with breast cancer conducted by the Sussex Psychosocial Oncology Group revealed an initial preference for oral endocrine medications.28 However, by the Sussex Psychosocial Oncology Group, poor adherence to tamoxifen, for example, has a significant association with increased risk of death from breast cancer.27

In trials of fulvestrant (250 mg monthly) versus anastrozole oral tablets (1 mg/day) for advanced breast cancer pretreated with endocrine therapy,9 Trial 0020 was an open-label study in which fulvestrant was administered as a single 5-mL IM injection. Trial 0021 was a double-blind, placebo-controlled study with fulvestrant administered as two 2.5-mL injections; anastrozole-treated patients in Trial 0021 received two placebo injections. The frequency of injection-site reactions appeared similar in both groups in Trial 0021 (4.6% for fulvestrant and 4.4% for placebo groups).31

FINDER 1 (Faslodex Investigation of Dose Evaluation in Estrogen Receptor-Positive Advanced Breast Cancer) and FINDER 2 (Faslodex Investigation of Dose Evaluation in Estrogen Receptor-Positive Advanced Breast Cancer 2) were designed to evaluate the efficacy and safety of three dosing regimens of fulvestrant, which would theoretically allow for lower overall injection volumes, has been investigated. Due to the solubility of the active drug, the maximum concentration formulated to date is 250 mg per 5 mL (50 mg/mL).30 In pivotal clinical studies of fulvestrant 250 mg/month, injection-site reactions occurred in 1% of treatment courses or 7% of patients treated with one 5-mL injection and in 4.6% of treatment courses or 27% of patients treated with two 2.5-mL injections.9,31 No sciatic nerve injuries have been reported in the literature for fulvestrant.

The fulvestrant dose approved by the US Food and Drug Administration was increased to 500 mg/month (two 5-mL injections) based on results from the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) trial.30 The CONFIRM trial found that 500 mg/month fulvestrant significantly prolonged progression-free survival versus 250 mg/month fulvestrant without increasing toxicity.30 The 500-mg/month dose is administered as two 5-mL IM injections (250 mg/5 mL each), one in each buttock, on days 1, 15, and 29, and once monthly thereafter.9 The additional dose of fulvestrant, given 2 weeks after the initial dose, allows steady-state blood levels to be reached within the first month of treatment.9

CLINICAL TRIALS SUPPORT LARGER DOSE
Robertson and colleagues combined and evaluated data from two trials of fulvestrant (250 mg monthly) versus anastrozole oral tablets (1 mg/day) for advanced breast cancer pretreated with endocrine therapy.9 Trial 0020 was an open-label study in which fulvestrant was administered as a single 5-mL IM injection. Trial 0021 was a double-blind, placebo-controlled study with fulvestrant administered as two 2.5-mL injections; anastrozole-treated patients in Trial 0021 received two placebo injections. The frequency of injection-site reactions appeared similar in both groups in Trial 0021 (4.6% for fulvestrant and 4.4% for placebo groups).31

FINDER 1, the incidence of injection-site pain was 31.1% in the 250-mg group, 21.6% in the LD group, and 30.4% in the 500-mg group.31 In FINDER 2, the safety profiles of the three regimens were similar.30 Injection-site pain was noted in all three treatment groups, with the lowest incidence in the 500-mg group (250-mg/month group, 10.6%; LD group, 10.0%; and 500-mg/month group, 6.5%).33

ON THE WEB
There’s more of this article online! Go to OncologyNurseAdvisor.com/injections to see this article with additional tables.
Patients with cancer are susceptible to bruising or bleeding; vigilant follow-up for factors that increase this risk is needed.

The CONFIRM study, a comparison trial of fulvestrant 250 mg/month (one 5-mL injection of fulvestrant plus one 5-mL injection of placebo) with 500 mg/month (two 5-mL injections: 500 mg on days 0, 14, and 28 of month 1, then every 28 days thereafter) for advanced breast cancer pretreated with endocrine therapy, showed no significant differences between the two doses in their safety profiles. Injection-site reactions occurred in 13.6% and 13.4% of patients treated with 500 mg/month and 250 mg/month, respectively. Fulvestrant was evaluated as first-line treatment in the Fulvestrant First-Line Study Comparing Endocrine Treatments (FIRST) study. Patients received fulvestrant 500 mg/month (two 250-mg injections on days 0, 14, and 28 of month 1, then every 28 days thereafter) or anastrozole 1 mg/day as first-line therapy for advanced breast cancer. Of the 102 patients treated with the fulvestrant regimen, six patients reported 14 instances of injection-site pain, for an incidence of 1.3% of all injections and 5.9% of patients. Fulvestrant (250-mg IM injection once monthly) was also examined as first-line therapy compared with tamoxifen (20 mg orally once daily) in a double-blind, randomized study. Injection-site reactions were reported by 2.9% (nine of 310 patients) receiving fulvestrant and 1.1% (three of 271 patients) receiving oral tamoxifen (placebo injection). Overall, the incidence of injection-site pain with fulvestrant 500 mg/month appeared to be similar to that observed in prior clinical trials of the previously approved 250 mg/month regimen.

**ADMINISTRATION BEST PRACTICES**

The Z-track method, historically applied to IM injections of irritating medications, can be used for all IM injections to reduce pain and prevent dispersion of medication into subcutaneous tissue. Other strategies for minimizing injection-site reactions are to alternate injection sites and to apply warm or cold compresses to the injection site. Fulvestrant should be stored between 2°C and 8°C, however, bringing it to room temperature prior to injection may aid the injection process. Patients with cancer are susceptible to bruising or bleeding; therefore, vigilant follow-up for factors that may increase the risk of bruising or bleeding, such as thrombocytopenia or anticoagulant use, is needed.

A breast cancer nurse specialist has reported patients often comment that they do not feel the injection when fulvestrant is administered with the Z-track method in the dorsogluteal site. Difficulty detecting the site postinjection was also reported, with no scarring after long-term (4 years or more) use. Best practices for administering fulvestrant such as depressing the plunger slowly and a slow injection rate can make IM injections less painful, regardless of the drug or injection volume. The high viscosity of fulvestrant serves to control its rate of administration, requiring approximately 2 minutes per injection (see the online version of this article for a summary of best practices).

### Table 1. Advantages and disadvantages of intramuscular injection sites

<table>
<thead>
<tr>
<th>Injection site</th>
<th>Maximum Injection Volume in Adult Patients</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deltoid</td>
<td>0.5-2 mL</td>
<td>• Easily accessible</td>
<td>Number and volume of injections are limited because of small injection-site area</td>
</tr>
<tr>
<td>Dorsogluteal</td>
<td>4 mL</td>
<td>• Patient only exposes arm</td>
<td>Major nerve and blood vessels present</td>
</tr>
<tr>
<td>Ventrogluteal</td>
<td>2.5-5 mL</td>
<td>• Free of nerves and blood vessels</td>
<td>Slow absorption</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>5 mL</td>
<td>• Can be used when other sites are contraindicated</td>
<td>Thick layer of adipose tissue</td>
</tr>
<tr>
<td>Vastus lateralis</td>
<td>5 mL</td>
<td>• Easily accessible</td>
<td>Discomfort with injection</td>
</tr>
</tbody>
</table>

Continued on page 36
In summary

The recent approval of fulvestrant 500 mg for the treatment of HR+ metastatic breast cancer in postmenopausal women who received prior antiestrogen therapy highlights the increased need for evidence-based IM-injection guidelines with best practices for delivering large-volume (3 mL or greater) IM injections. The practical recommendations discussed in this article are supported by current evidence from the literature, as well as from nursing experience within the clinical setting, and could be considered in future guidelines for large-volume IM injections.

Evidence-based guidelines for large-volume IM injections will also depend on rigorous research. One area for future research is to determine the optimal amount of time needed to administer large-volume injections, as medications in viscous solutions may take longer to inject. Optimal practices for patients of different weights and sizes should also be investigated because IM injections may be more difficult to administer in heavier patients and older patients may have low muscle mass or integrity. The potential benefits of alternating injection sites, such as between the ventrogluteal and dorsogluteal sites, in order to lessen patient discomfort should be examined as well. Finally, future studies should assess the validity of clinical observations. For example, in our practice, we noted that occasionally patients have discomfort upon sitting after a dorsogluteal IM injection. Two nurses administering fulvestrant simultaneously (ie, one nurse per injection per buttock) has been helpful for patient comfort in our experience. Finally, we found that massaging the area during and after an IM injection helps to prevent and relieve pain.

With proper technique, appropriate patient education, and adequate follow-up, IM injections offer a safe and effective route of medication delivery that supports treatment adherence and effective monitoring of adverse events. Further research and adherence to evidence-based best practices will undoubtedly enhance the efficacy and safety of this administration route as well as increase patient and clinician comfort.

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