

Subcutaneous IgG Replacement Therapy

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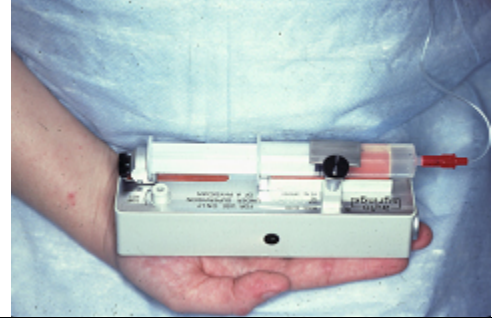



Cleveland, Ohio 44106

What is subcutaneous Ig?

Subcutaneous literally means: “under the skin”. Subcutaneous injections of gammaglobulin were used by Bruton to treat the first patient diagnosed with agammaglobulinemia, in the early 1950's. Subsequently, intramuscular (IM) injections of gammaglobulin were used in a large study in the United Kingdom and this became the standard route of administration of IgG for patients with antibody deficiencies. IM “gammaglobulin shots” were also widely used during the 1950's in patients without PIDD to prevent outbreaks of infectious diseases such as measles and polio, and were sometimes given to premature babies. The type of gammaglobulin used by Bruton and in the study in the UK is called Immune Serum Globulin (ISG). It is produced as a 16% solution, as compared to most IV preparations, which are used at 5 or 10%. The 16% ISG is still used for preventing hepatitis A infection for travelers, and occasionally to prevent infectious disease outbreaks in non-immunized populations. In the late 1970's, before intravenous immunoglobulin became available, Dr. Berger and his colleagues used a small battery-powered pump to give 16% ISG to a patient who would not take her ISG shots because they were quite painful. She also had had bad reactions to plasma transfusions, the only alternative to IM shots available at that time (1). The pump gave the ISG slowly- over several hours- and eliminated the pain associated with the deep IM shots. This patient and several others tolerated the ISG quite well using this slow subcutaneous method with the pump, shown in figure 1. This first young woman who used the pump for ISG soon got married and became pregnant, and took subcutaneous ISG throughout her pregnancy. She used up to 20 cc (which contains 3.2 grams of IgG) every day in the last months of the pregnancy (2). This allowed her to receive over 22 grams of IgG per week. Both the mother and baby had normal IgG levels at the time of birth, meaning that enough IgG had been given to the mother to transfer across the placenta and give the baby a normal level as well.

After these initial descriptions of the use of pumps to slowly give 16% ISG, the subcutaneous route became widely used in other countries, particularly Sweden, and many more papers on this route have been published (see a list in reference 3). Ann Gardulf and her colleagues in Sweden found that many patients could take the subcutaneous infusions quite rapidly, and have published many papers on the safety and utility of both home and hospital-based subcutaneous infusions (listed in reference 3). Other authors have reported on the use of the subcutaneous route in children (reference 6 and additional papers listed in reference 3). These papers illustrate the great flexibility of the subcutaneous approach. Subcutaneous is still the major route of IgG treatment in Sweden, and overall, is being used by more than 10% of the PIDD patients in a recent survey across the European Union countries (7). In the US, IV preparations were introduced in the early 1980s and have become the most common way to take IgG. However, Dr. Stiehm and his colleagues at UCLA showed that PIDD patients who had severe reactions to IM or IV infusions could tolerate their IgG quite easily when it was given by the subcutaneous route (8,9). Other doctors have also found that this route of administration may have fewer side effects than

standard IV infusions (summarized in table 1 in reference 3) and may be easier to use in patients in whom starting and maintaining IVs is difficult (10,11). For these reasons, many patients have been allowed to self-infuse their IgG at home using the subcutaneous route. Ann Gardulf and her colleagues have done studies that show that the ability to self-infuse creates a sense of autonomy, which has positive effects for many patients (5).

	<p>Figure 1: This is patient 1 in reference no 1, who is also described in reference 2, holding the Autosyringe which she used to infuse 10 or 20 cc of 16% ISG subcutaneously. A 10 cc syringe containing the ISG is in place and there is a 25-gauge butterfly infusion set attached to the syringe. This exact type of pump is no longer available.</p>
	<p>Figure 2: This shows a 25-gauge Butterfly needle in the patient's skin on the side of her abdomen. The needle is inserted at about a 45-degree angle so that its tip is at least ½ inch below the skin. There were no problems in pumping the 16% ISG through this small needle.</p>
	<p>Figure 3: A gauze pad was rolled up under the “wings” of the butterfly to keep it at the steep angle and both were taped in place. Nowadays, subcutaneous infusion sets are available which have the needle already mounted at a 90° angle, so that the tip penetrates to the right depth. (Click on Pumps and needles to see examples.)</p>
	<p>Figure 4: The patient wearing her pump and taking the infusion while she was able to walk around and do housework or other activities.</p>

Several 16% IgG products are available in Europe, and there is now one specifically licensed in the US for administration by this route, Vivaglobin[®]. Some authors have described subcutaneous infusions of 16% ISG, which is licensed in the US for IM use (12). Other papers have described subcutaneous infusions of products licensed for IV use (10-12). Subcutaneous infusions are often

given with the use of small pumps like the one shown above, so that the IgG is injected gradually because there may be milder local reactions or less local pain if the skin is stretched slowly rather than quickly. Some of the pumps that have been used are shown in the [link “pumps and needles”](#). Some of these pumps use a motor to push the plunger of a regular syringe, while others use rollers to pump IgG from a plastic reservoir or small bag. In general, 20-40 ml (cc) may be infused into a single subcutaneous site in adults, with lower volumes per site in children, depending on their size. Many patients will infuse their IgG into two sites at once, using a tubing set with a y-connector, which infuses via 2 needles at once. Favorite sites include the front or sides of the abdomen, the thighs, or the backs of the upper arms (see the link to the NIH publication on subcutaneous injections marked by the asterisk * below for a diagram showing good sites to use and general instructions on sub-cutaneous injections). If more concentrated IgG solutions (like 16%) are used, the volume that must be infused is lower than if less concentrated solutions are used. For example, to take 5 grams of IgG would require 100 ml (cc) if a standard 5% IV solution is used, 50 ml (cc) if a 10 % solution is used, but only 31 ml (cc) if a 16% product is used. It is obviously much easier to take the latter volume, approximately 1 ounce, by the subcutaneous route, as opposed to trying to take 100 ml by this route. In contrast, once an IV is started, the volume administered may be less critical and larger infusions of more dilute products would be more easily given by that route.

Some patients prefer to take small doses of IgG subcutaneously without using a pump. They may inject a dose like 10 ml over 5-15 minutes into a single site, using a butterfly needle. Patients who prefer this method may have to take their IgG several times per week, or even every day, but the short time of each injection might make this more convenient for them.

Click Here To See Different Types of [Pumps and Needles](#) Which Have Been Used To Give Subcutaneous Ig

Side Effects of Subcutaneous Ig:

Subcutaneous infusions rarely cause severe systemic reactions, but many patients may develop a large hive at the infusion site. Itching or burning associated with this may be prevented or relieved by the use of antihistamines such as Benadryl^R, but few patients require other pre-medications for subcutaneous infusions. Studies have shown that most patients who have local reactions when they begin subcutaneous injections have fewer reactions with time as they continue with this route. Most doctors like patients to have medicines like adrenaline (also called epinephrine) available, just in case a severe allergic reaction (called anaphylaxis) occurs. This is conveniently kept available as an Epi-pen^R or Ana-kit^R, which might also be prescribed for patients with food allergy or who have had severe reactions to insect stings.

Differences in Dosing of Subcutaneous vs. IV Ig: In order to receive their total monthly IgG dose, most patients who use the sub-cutaneous route must take infusions once or twice every week. For example, a patient now receiving 24 grams of IgG by IV once a month might receive about 6 grams once a week (4 times a month) by the subcutaneous route. Taking smaller doses of IgG more often results in less dramatic changes in the amount of IgG in the blood (the serum IgG level) than the high peaks, which occur right after a large IV infusion is given. Frequent subcutaneous doses also even-out the low trough, which occurs three or four weeks after monthly IV infusions, just before the next dose is due. Making the serum IgG level more even

during the month may decrease the amount of side effects experienced by many patients. (Figures 5-8).

In the one large study of a subcutaneous preparation that was done in the USA, the FDA required that the total amount of IgG in the blood stream at all times had to be the same whether it was given by the IV or subcutaneous route. Since IV infusions put the IgG directly into the blood stream while it takes one or two days for the subcutaneous IgG to get into the blood stream, this meant that a higher dose had to be given by the subcutaneous route to equal the high amounts that are present in the first day or two after the IV infusions. It is also possible that some of the IgG given by the subcutaneous route never makes it into the blood stream. Because the studies in the US were done according to the FDA guideline, the prescribing information for Vivaglobin^R states that the total dose should be 137% of the previous IV dose. In Europe, the regulatory agency, which is like the FDA in the US, does not have this requirement, and similar total monthly doses are used regardless of whether it is used subcutaneously or IV. In general, doses of 100-2900 mg/kg/week (400-800 mg/kg/month) will be adequate for most patients, but as with IV infusions, the dose and schedule needs to be individualized for each patient.

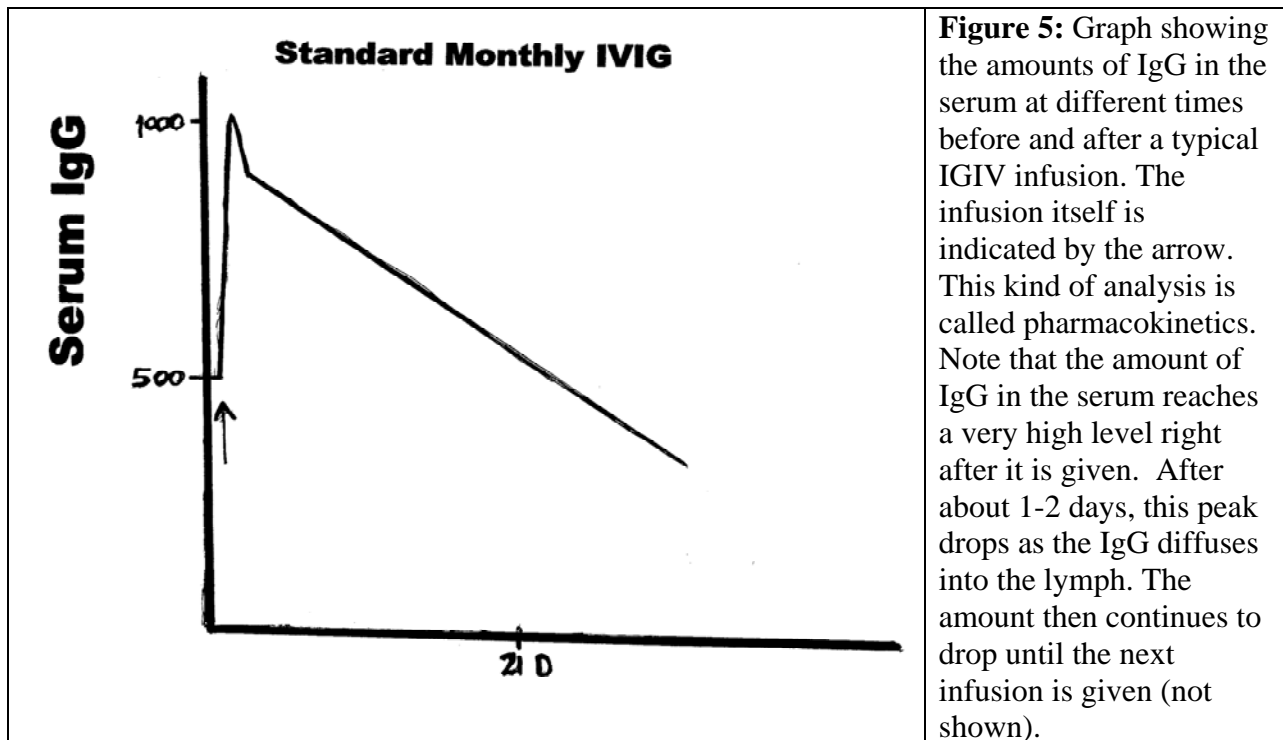


Figure 5: Graph showing the amounts of IgG in the serum at different times before and after a typical IGIV infusion. The infusion itself is indicated by the arrow. This kind of analysis is called pharmacokinetics. Note that the amount of IgG in the serum reaches a very high level right after it is given. After about 1-2 days, this peak drops as the IgG diffuses into the lymph. The amount then continues to drop until the next infusion is given (not shown).

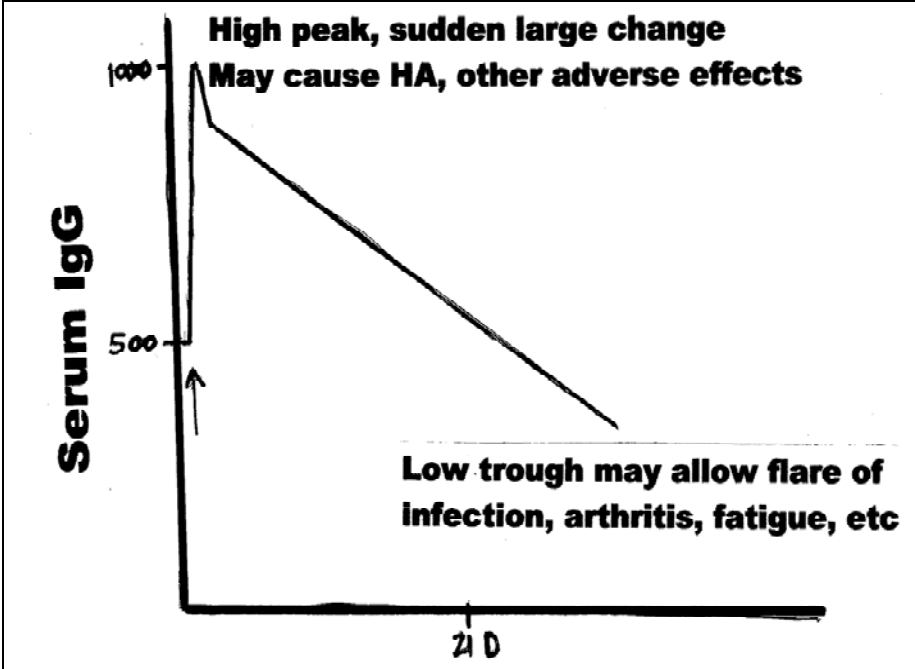


Figure 6: The high peak IgG level may cause side effects in some patients. Also, the low level to which the IgG falls by the end of three or four weeks may not be enough to keep the patient feeling healthy at that time. The lowest level reached before the next dose is called the “trough”

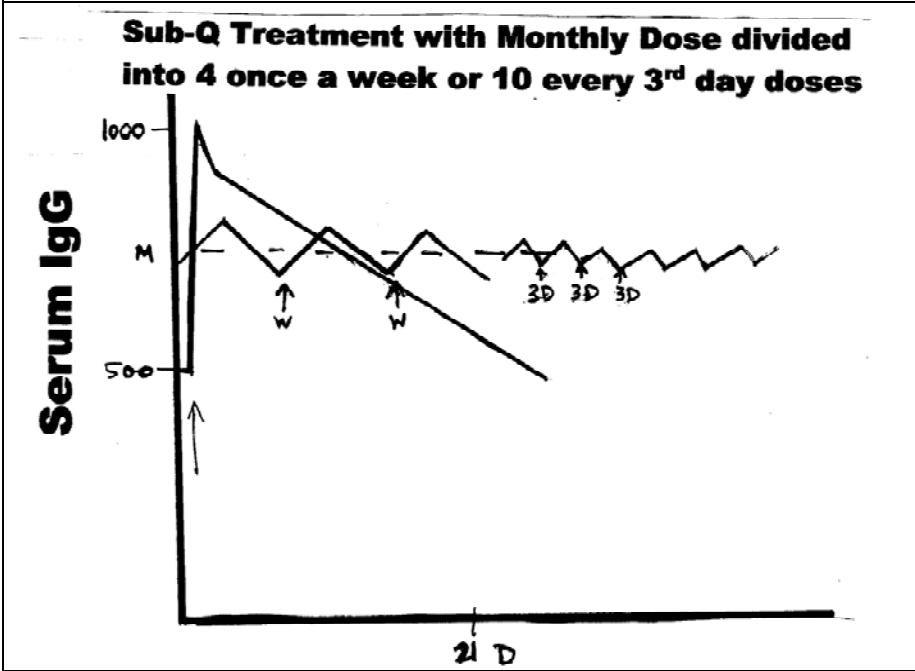


Figure 7: If the same total amount of IgG is divided into smaller doses which are given more often, the peak will not be as high, and the trough will not be as low. This may decrease the side effects felt by some patients.

Serum IgG Levels in 34 year old Male with XLA

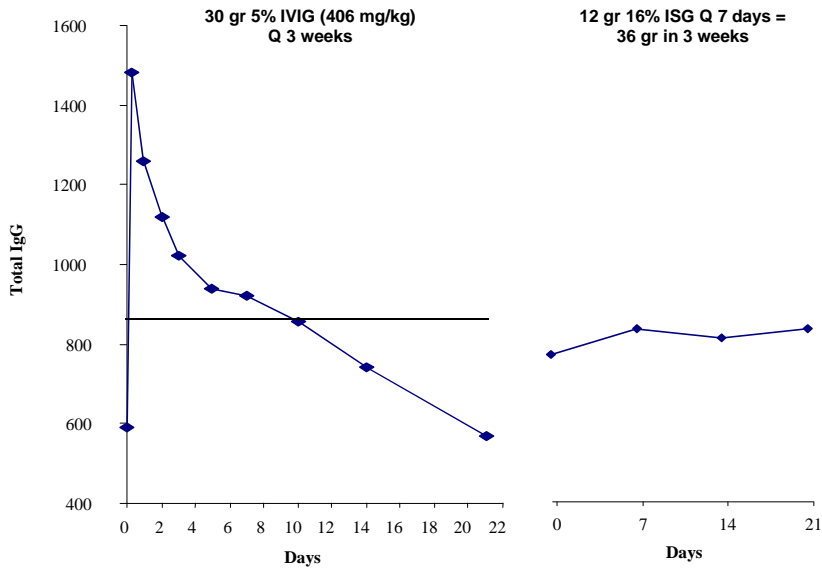


Figure 8: The left part shows actual serum IgG levels in a patient with X-linked agammaglobulinemia (XLA or “Bruton’s Disease) who makes no IgG on his own. His trough just before an IV infusion was just under 600. The infusion boosted his IgG to 1500, and then it fell to less than 600 again. The solid line indicates the average IgG level during the whole 3-week period. The right side shows what happened when patient was switched to weekly subcutaneous infusions. This was part of the study of Vivaglobin^R, which was designed to maintain the same average amount of IgG in the blood for the whole time. Notice that a higher dose of IgG was required for the subcutaneous route to equal the amounts in blood stream after the IV dose, but on subcutaneous, the trough was much higher- over 800, compared to less than 600 on IV.

Local Reactions at the Sites of Sub-cu IgG Injections: Most patients will be injecting ½ to 2 ounces into each subcutaneous site. Depending on the speed of the injection, this fluid may already be diffusing away as it is given, or some or all of it may remain in place and diffuse away over several more hours. In some patients, particularly when sub-cu is just being started, there may be some redness or irritation associated with this, but in others those symptoms do not occur. Some patients report itching or burning associated with the redness, in which case, benadryl or other antihistamines may provide relief. Redness, irritation or other local symptoms tend to become less prominent with continued use of the sub-cutaneous route. In most cases, the swelling and any redness or other symptoms will be completely gone in 12 hrs.



Figure 9: Here is a patient receiving IgG from a Freedom 60 pump into 2 sub-cutaneous sites on the thighs.



Figure 10: Here is a closer view of the needles in place.



Figure 11: Here you can see the typical appearance of the sites at the end of the infusions. Each site has received 3 grams of IgG in 20 ml. There is some swelling due to this volume but minimal redness or other tissue reaction. The swelling is painless and will dissipate over a few hours.



Figure 12: Here you can see a "Soft-set" needle in an abdominal site.



Figure 13: Here you can see some local redness in addition to swelling at the abdominal sites. Many patients are not bothered by this, but some complain of some burning or itching. That may be reduced by treatment with benadryl. In any case, this type of reaction disappears within a few hours and leaves no residual effects. The redness and reactions seem to get milder or disappear with time as the patient continues with the infusions.

Summary: In summary, “subcutaneous IgG” refers to the administration of IgG under the skin rather than into the vein. Usually, smaller doses are given more often with subcutaneous as compared to IV Ig. There is great flexibility in choosing the exact schedule and treatment plan, since many patients can give their own infusions at home. Patients still need to follow-up with their doctors at regular intervals. A new product containing (16%) concentrated IgG which is specifically licensed for subcutaneous use, Vivaglobin^R, became available in the US in March 2006. A variety of IgG products currently licensed in the US for use by the IM or IV route have also been successfully given by the subcutaneous route (10-12).

FAQ

Does taking the IgG sub-cu make it act differently in my body?

No: Once they are adsorbed into the bloodstream, the antibody molecules basically act the same way. Studies with antibodies to the Rh blood group (given to Rh negative pregnant women to prevent them from making antibodies that might harm future Rh+ babies) have shown that giving them by different routes is equally effective. However, IgG molecules which are clumped together, and/or impurities in the preparations, may cause side effects when they are given directly into the blood stream. These clumps (called “aggregates”) or impurities may react differently under the skin. This may be one of the reasons there seem to be fewer reactions when IgG is given sub-cutaneously rather than intravenously.

Are there preservatives containing mercury (Thimerosal) in the 16% ISG ?

No: Neither Vivaglobin^R (CSL Behring) nor the only other 16% ISG currently sold in the USA, (Gammastan^R) (Talecris) contains thimerosal or any other preservative containing mercury. Therefore, once the bottle is opened by putting a syringe through the stopper, the IgG must be used within hours. Partial doses should not be saved, even in the refrigerator. These products are treated the same way as the IV preparations (solvent/detergent (S/D) treatment or pasteurization and alcohol treatment) to inactivate potential viruses.

How does the cost of sub-cutaneous IgG compare with intravenous IGIV ?

For most patients other than small children, the main part of the cost is for the product itself. Since subcutaneous and IV products come from the same blood donors and are made by similar processes, the cost per gram is about the same. Therefore, the overall costs for both routes are likely to be pretty similar. If the sub-cutaneous route is used at home, without participation of a nurse, costs that would be associated with a home-infusion nurse or which might be charged in a hospital or infusion center will be saved. In that case, there is less traveling time and the infusions will usually be given at times that do not interfere with work or school. That may be important to certain patients, and may preserve “sick days” or income. Most patients who self-infuse sub-cutaneously use a pump. Depending on which type of pump is used, the price to buy the pump may be from \$200 to \$2000. Some medical equipment companies may rent the pumps for a monthly fee. Supplies for sub-cutaneous infusions might cost \$5.00 to \$20.00 per infusion, depending on exactly what is used.

Click here to link to: [Pumps and Needles](#) (some pumps and subcutaneous needles/infusion sets which have been used for IgG in the US)

Links to other sub-cu sites (If you are reading this in Word, hit control and click on the link):

www.Vivaglobin.com

[Guidelines for sub-cutaneous IgG use in the UK](#)

[Subcuvia, a product sold by Baxter in Europe for Sub-cu use](#)

[Launch of Subgam, a subcutaneous preparation sold by BPL for use in England](#)

*Patient Information Publications. Giving a Subcutaneous Injection.
www.cc.nih.gov/ccc/patient_education/pepubs/subq.pdf.

UK Primary Immunodeficiency Association. Understanding Subcutaneous Infusion.
www.pia.org.uk/publications/general_publications/subcutaneous_infusion.htm






Dr. Berger's Teaching Slides 2007

References and links for PDFs (notations in blue are links: hit control and click at the same time to connect and read).

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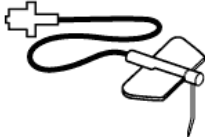



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INFUSION PUMPS

	Equipment Name	Manufacturer	Product Information	Features / Specs
	Auto Syringe AS50 Infusion Pump	Baxter	Product Information	<p>Size: 3.4" x 2.6" x 10" (8.6 x 6.7 x 25cm) Weight: 3.2 lb (1.45 kg) Syringes Accepted: B-D¹ plastic 1-60 mL Monoject² 1-60 mL Turumo³ 1-60 mL</p> <p>(1 Becton-Dickinson and Company, 2 Sherwood Medical, 3 Terumo Medical Corporation)</p>
	CADD-Legacy® Ambulatory Infusion Pump	Smiths-Medical	Product Information	<p>Size: 1.6 x 3.8 x 4.4 in (4.1 x 9.5 x 11.2 cm) Weight: 13.8 oz (392 grams) Administration Sets: CADD Administrations Sets</p>
	Crono Pump	Intra Pump Infusion Systems	Product Information	<p>Size: 3 x 1.9 x 1.1 in. (77 x 48 x 29 mm) Weight: 115 gram (battery included) Syringes: Dedicated with 10 or 20 ml capacity</p>
	Freedom60 Syringe Infusion System	Repro-Med Systems, Inc.	Product Information Nurse Instructions	<p>Size: 12" x 2" x 4" Weight: 14 oz. (397 gm) Syringes: Std. 60cc Administration Sets: Freedom 60 Sets</p>
	Graseby Medical Model MS16A Desferal Therapy Syringe Driver	Marcac Medical	Product Information	<p>Size: Weight: 6 oz. Administration Sets: Graseby Infusion Sets</p>

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SUBCUTANEOUS NEEDLES


	Equipment Name	Manufacturer	Manufacturer Website Link
	Sub-Q Sets	Med Stream	
	Sub-Q-Set Subcutaneous Infusion Sets	Baxter	Product Information (Page 23)
	Subcutaneous Infusion Set	Smiths-Medical	Product Information
	Sof-Set Ultimate QR® and Sof-Set Micro QR® Pump Infusion Sets	Medtronic Minimed	Product Information
	SET-PUMP 30" MB 2M/LL PINCH50/CS, CS	Medstream	Product Information
	Microbore Y-Type Catheter Extension Set	Baxter	Product Information (Page 16)

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ACCESSORIES

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SUBCUTANEOUS NEEDLES

	Equipment Name	Manufacturer	Manufacturer Website Link
	Rapid Fill Connectors	Baxa	Product Information

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