

### 3.2.2.3.2.14 Bulk apomorphine

(Please note: this is an updated version of an article written in 2001. In 2001, I purchased bulk apomorphine from a chemical supply house. The apomorphine I bought was manufactured by Sigma Aldrich. I have no doubt that it was manufactured in accordance with strict quality controls, but it was not considered “pharmaceutical grade”. I do not recommend that people purchase apomorphine which is not pharmaceutical grade, and I myself did not reorder. Instead, I later purchased proper apomorphine sublinguals manufactured for human consumption in accordance with US pharmaceutical regulations, and I obtained a proper prescription for it.

Suppliers of official Uprima that sell the medication on the Internet charge outrageous prices, 80 Pound Sterling (about 120 US dollars) for four doses of 3 mg apomorphine (30 US dollars a dose!). And, according to my experience, the 3 milligram of apomorphine which in the most potent Uprima version are not as generously measured as Pfizer’s Blue.

100 milligram of sildenafil citrate cost some 10 to 12 US dollars, but half of such a tablet does the job for most men. So, the actual price per dose of sildenafil citrate comes down to 5 to 6 US dollars, which I consider still affordable.

Because of the high price, I myself have started using apomorphine regularly only after I had come across an address through which I could receive apomorphine at less than 10 percent of the official Uprima price, which then is a bargain for sexual enhancement.

Unlike sildenafil citrate apomorphine is not a new medication. It has been around for decades for the treatment of Parkinson’s and as an emetic (a medication used to induce nausea and vomiting). This is important as far as patent rights are concerned.

Sure, Uprima is a patented medication. But the patent covers just the use of apomorphine in the treatment of erectile dysfunction, and the delivery method as sublingual tablets. Apomorphine itself is no longer patented.

For this reason, trade in apomorphine itself is much less restricted than, for example, trade in sildenafil citrate, which is a new substance.

Bulk apomorphine can be ordered from large chemicals companies. I once purchased supply of 250 mg that was manufactured by Sigma-Aldrich ([sigma-aldrich.com](http://sigma-aldrich.com)), but I bought it through a local chemicals distributor in Asia.

There is an online store at [sigma-aldrich.com](http://sigma-aldrich.com), but looking up a chemicals supplier in the yellow pages of any large city may reveal a source closer to home. Furthermore, Sigma-Aldrich is not the only chemicals company through which apomorphine can be purchased online.

One has to be aware that the dosages used of apomorphine are very, very small. Uprima is sold as sublingual tablets of 2 or 3 milligram apomorphine. The therapeutic dose is in the range of 1 to 10 milligram apomorphine.

Amounts of 2 or 3 milligram are of course hard to measure if one doesn't have access to laboratory equipment. I use a small precision screwdriver to quantify dosages. The tip holds approximately 2milligram, as I established by counting the purchased dosage of 250 milligram into some 120 portions. You do not need a microscope or magnifying glass to see a dosage of 2 milligram.

The delivery route of apomorphine is very important. If it is just ingested, it is very likely to cause nausea. The delivery has to be sublingually, so that the apomorphine reaches the blood stream fast (in the treatment of Parkinson's, apomorphine is usually injected, which, of course, is even faster).

To the best of my knowledge, there is nothing terribly high-tech in supplying dopaminergic agents via the sublingual route. For the manufacture of sublingual tablets, one just has to use a base that dissolves fast and at the same time is firm enough to be pressed into tablet form. Even simple glucose could do the job.

The dopamine agonists apomorphine, bromocriptine, and lisuride are all fairly complex molecules. But they have the ability to pass through

the mucous skin of the oral cavity, which is why they are suitable for sublingual application. A hydrochloride form (salt) of the active ingredient may be used for convenience, but apart from that, the apomorphine or other dopamine agonist is not chemically modified for sublingual usage.

I myself just placed the amount of a few milligram (about 5) of apomorphine below my tongue... unmixed with any sublingual facilitator.

## Feedback

While I have had no problem ordering Sigma-Aldrich apomorphine in Asia, those who want to order it in the US may face some problems, as has been reported by a reader who tried it. This has been caused by a published abuse of their supply line.

"I tried to order some apomorphine using Sigma-Aldrich's online order system. Placed the order online with no problem. They call you back to do a screening on all new accounts however, to see if your "facility" is qualified to handle the chemicals, and if the end-use is acceptable. I thought I was very good and creative on this one. I said that I was a dog breeder, and used apomorphine as an emetic for poison overdose (it has been used this way by vets for years).

They said they are not allowed to sell apomorphine for that application since their apomorphine is reagent grade and not pharmaceutical grade, and this grade is not FDA-approved for end use in humans or animals, unless as part of an experiment where the animal is destroyed. So much for my cover story.

So if anyone is going to make it past the screening, they have to say they are a research company or something, and make it acceptable. Even then it might be hard – they may ask for a business license and articles of incorporation as proof. They screen due to increased scrutiny since the Scientific American expose where SciAm ordered all the stuff needed to make Sarin gas from Sigma-Aldrich, with no questions asked, and then published an article about how easy it was to order stuff to make nerve gas over the web. Yikes!!

The Sigma-Aldrich representative pointed out that what they supply

is reagent grade, not pharmaceutical grade. The question is whether this makes a difference, quality-wise. Please see the following expert considerations:

“Well it is a small amount being ingested and the synthesis isn’t terribly complex, so the risk may not be large, but who knows what synthesis method they are using. If it involved highly carcinogenic solvents such as benzene or toluene along the way there would be traces left in the final product. Also heavy metals like lead, arsenic, or cadmium could be present. Biological toxins could be present in small amounts. The morphine used as the starting material would also not have to be pharmaceutical quality for the Sigma-Aldrich apomorphine, so any impurities in it would be carried through. Sigma specs their stuff as 99% pure, so there is 1% of a bunch of things in there.

With pharmaceutical grade material there are all kinds of restrictions on what kinds of processes and reagents can be used, and the resulting purity required, with FDA oversight and audits as well to insure that each batch meets the specs. Same applies to all materials and solvents used – all have to be traceable and all suppliers have to meet cGMP specs all the way up the chain.

Without getting disclosure from Sigma-Aldrich as to how they make this stuff and what materials are used as sources, and what impurities are in the final product, there isn’t really much of any way to know how much risk is involved. You could get a small sample tested somewhere via gas HPLC spectroscopy and mass spectroscopy to see what else is in the stuff, both organics and inorganics, and perhaps assume that future batches will generally be similar.

You also don’t know what shelf life to expect or how to store it. It should be pretty stable stuff but it might degrade to dangerous degradation products in a year or two, less if hot and humid. Again pharmaceuticals are all characterized for stability under various conditions as part of the development and registration process and they are packaged and labeled accordingly.

I think it is primarily a regulatory issue, but as I indicated above the actual synthesis, reagents used, and final impurities could also be significantly different.

Apomorphine is used in pharmaceutical grade for veterinary purposes – to induce emesis in dogs that ingest poisons accidentally, by placing a large dose right in the eye. You might be able to find a source through some veterinary supply place and get better stuff this way. It should be very cheap in this form as well. Might come as an injectible bottle in liquid form however, rather than a powder, I don't know, but with a small syringe you could just place a drop or two or whatever amount is needed sublingual to get the right dose.

Also of course it is available in injectible form for treating Parkinson's disease, and this would be fully human pharmaceutical quality. Probably very hard to get however, but maybe not too hard where you are. More expensive this way I am sure but probably still an order of magnitude less than Uprima.”

Further research

I have written to Sigma-Aldrich to inquire whether they just produce reagent apomorphine, or whether they also sell pharmaceutical-grade apomorphine to companies who then market this apomorphine for the treatment of humans or other animals. I didn't word my inquiry so directly, but rather put it the following way:

“As a journalist and potential buyer of Sigma-Aldrich shares I would like to know whether your company only sells reagents to the pharmaceutical industry, or also bulk pharmaceutical-grade products (especially those of which patents have expired) which are then just repackaged as drugs and marketed under the name of the pharmaceutical company you supply? If you do sell bulk pharmaceuticals, is there an overview of volumes?”

I received the following information from Sigma-Aldrich:

“Sigma-Aldrich sells reagents to pharmaceutical companies for their use in development. We do not sell bulk pharmaceuticals. The pharmaceutical and biotechnology industry provides about 40% of our annual revenue with the remaining 60% coming from

universities, government, the chemical and other industries and the diagnostic market.”

I have then sent the following inquiry to a chemical engineer who is an expert on production standards:

“Chemical companies (such as Sigma-Aldrich) produce the same chemicals that are widely used in the pharmaceutical industry. They produce in accordance to current Good Manufacturing Practice (cGMP), but sell these chemicals as reagent grade, not pharmaceutical grade.

“In your opinion, what would be the quality difference to expect in chemicals produced by chemicals manufacturers adhering to cGMP guidelines, and pharmaceutical companies producing these chemicals in pharmaceutical grade.”

I received the following answer:

“Aldrich has a GMP manufacturing unit but I doubt that every chemical in the catalog is made to GMP standards. That is not to say that the chemicals they sell are not very pure which I’m sure they are.

“The quality difference of items made to GMP standards are: that they would come with a C of A, be made according to a validated procedure (at least three times), have a known stability profile, be expiration-dated, be labeled properly with only pre-established claims, etc.

“Other than consistency batch to batch, a chemist should not see any difference especially if the company is certified to ISO9000 or has another internal quality program such as TQM, six sigma, etc. which almost everyone does.”

Sigma-Aldrich is of course not the only possible supplier for apomorphine, and other suppliers do deal in pharmaceutical-grade chemicals.

One of the best web sites on matters of interest to purchasing chemicals is:

<http://members.tripod.com/~ChristopherMarrs/>

Please specifically see the following page:

[http://members.tripod.com/~ChristopherMarrs/GMP\\_Drugmanufacturer.html](http://members.tripod.com/~ChristopherMarrs/GMP_Drugmanufacturer.html)

The page lists many companies that sell chemicals, including chemicals designated as pharmaceutical grade.

Additional sources (contributed by J.)

I found two sources so far of pharmaceutical grade apomorphine:

MacFarlan Smith Pharmaceuticals in Edinburgh Scotland

<http://www.macsmith.com/>

They would have a large minimum order requirement – maybe a kilo or more.

Gallipot Inc. in St. Paul Minneapolis, USA

No web page but info here:

<http://members.aol.com/mefrancom/gallipot.htm>

Small quantities should be fine here.

A third source which is not pharmaceutical grade but interesting for another reason (see below) is ICN Pharmaceuticals:

<http://www.icnbiomed.com> (Do a search for apomorphine there)

MacFarlan Smith would be an excellent and reputable source – a major supplier, but they deal in bulk only.

“I also found info that apomorphine quickly absorbs water and

degrades, turning blue-black in color within a few months to a year. You need to keep it dehydrated in a dessicator to have it remain stable.

“I had another thought about your dose level. Apomorphine is chiral (has a handedness, and rotates polarity of light when in solution) as are most biologically active chemicals – there is an S+ and R- form. The material from Aldrich is certainly a mixture of the two. It is likely that to reduce nausea, TAP/Abbott have chosen to use only the biologically active form, which is the R- form, so that side effects from the inactive form are eliminated. This would reduce dosage by 1/2. ICN sells the R- form, which of course is at a much higher price, \$28 for 100 mg, but still cheap. Not pharmaceutical grade however.”

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I have received another reader's mail on the quality of non-pharmaceutical grade apomorphine:



“By the way, I am not very knowledgeable about chemicals, but I am surprised that your expert expressed a concern about benzene and toluene. Toluene is a common solvent in all sorts of glues and paints, and many painters and factory workers inhale large quantities of it every day. Benzene used to be a popular solvent (and large quantities were inhaled by lots of people), but it is now considered carcinogenic. Nonetheless it is still widely used in manufacturing all sorts of things. The carcinogenic effects are rather weak. The amount of benzene or toluene that you might ingest in a few mg of apomorphine would be tiny, so even if you did it every day I can't see that it would be dangerous. Note that this is a just lay person's opinion. I don't know anything about other possible impurities.”

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