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GBS ……..CIDP

INFORMATION

STICK WITH IT
SLOW BUT SURE
NEWSLETTER OF THE IN GROUP: THE INFLAMMATORY NEUROPATHY SUPPORT GROUP OF VICTORIA INC.
Supporting sufferers from acute Guillain-Barre Syndrome(GBS) & Chronic Inflammatory Demyelinating Polyneuropathy(CIDP)

The Guest Speaker for our February meeting was Scott Dobbie from Octapharma Australia Pty. Ltd., who spoke on their product 'Octagam', a similar product to 'Intragam' which is well known to our members as a form of intravenous immunoglobulin frequently used to treat both GBS and CIDP.

It's a pleasure to come and talk to you as a representative of the blood industry in Australia. There are a couple of things I'd like to talk about tonight.

Blood is a very precious and important resource in health care. It has many medicinal purposes. It's given freely by donors and the Red Cross call it "the gift of life" and it's an absolute pleasure for me to be working in an industry helping people manage their diseases and provide treatments and cures for many patients.

The purpose tonight is to give you an overview of the industry. There have been a lot of discussions in the media recently because of another review of refractory services in Australia which I'll talk to you about later. It is a hot topic at the moment with lots of information and interest by people in the blood sector reform. It's a complex industry, heavily regulated and heavily scutinized, and it does mean that the way the commercial area works is under a lot of government control and to operate you have to work at the very highest level of competency and ethical standards within Australia and around the world. The business of blood in Australia and around the world is one that is highly regulated, highly complex and also very ethical.

I'll give you a talk on the blood industry and a refresher on the blood sector, then I'll introduce Octapharma and the product which we are currently supplying into Australia which is an IVIG called Octagam which is why I'm here tonight. There may be patients at the moment that may be seeing different brands appearing in the market place and obviously doctors might be allocating, through the Red Cross blood service, different products. Until just a few years ago there was only one product of choice in Australia produced by CSL and that was the only product available. Now, for various reasons, there are a couple of products available and it is useful as consumers and as patients to actually be aware of what those products are, be comfortable with where they come from and how they are produced, so that if you do get offered a different treatment or a different product to what you may have received in the past it's not a scary situation for you.

Obviously when someone from the community goes along to the Red Cross and donates some blood, blood is made up of a mixture of various things. Blood has a number of cells that have various functions and those cells are in a watery liquid called plasma which is what holds it all together. The plasma when you spin a test tube of blood it is the yellow straw coloured liquid that tends to form which makes up about 50 percent of the blood volume in our bodies. Of plasma 90% is actually water

but it contains the most components of blood itself so there are various sugars, salts and hormones, various waste products, cells, clotting factors, and proteins. It is the proteins included that contain immunoglobulins and that we are interested in with IVIG because these proteins offer a lot of therapeutic benefits to patients with various diseases. The proteins, or the immunoglobulins contained in the plasma, are very small and only a tiny amount of protein is what we extract for medicinal purposes. So when someone donates blood the plasma is separated from the red cells and other components of the blood and it is then provided to a fractionator to actually turn it into the various products. I should mention, in the course of making these products there is a whole range of products that can be made from this plasma, so IVIG is only one component that is used for medicinal purposes.

A question often asked when patients are given a bottle of IVIG is how many donators does it take to make that bottle and in the case of Octagam a 10gram bottle requires approximately 300 to 350 donors to contribute to making that finished product. It does require a lot of donations to extract the small amount of proteins, the active components that we are looking for, to be of medicinal value. This is why it is so precious and valuable from a health care perspective because it does take a lot of effort to extract the important bits.

I have already mentioned the Red Cross Blood Service who has the expertise in the collection and distribution of blood products in Australia. They have a very important role and they do a fantastic job. It is an incredibly complex and difficult process to collect the blood, make sure the donors donate regularly and to have adequate funding to collect the blood and then to ensure they can distribute the blood and supply the finished products to those who need them and they do an excellent job in that regard.

Australia has a policy of "self sufficiency" so we are trying to collect blood from Australians and then to supply the products produced from that blood back to Australian patients and that goal of self sufficiency is one that is in place in many countries around the world that they try and use the population of that country to provide the blood for products that will be used. The problem is that in a county like Australia, where the demand for the products exceeds the ability of the Red Cross to collect enough blood to make enough product, we have problems with shortages or problems with not having available certain products to treat certain conditions. That is a challenge for Australia and for the Australian government to manage, however they have put into place certain methods and certain things to try and manage that as best they can. The other biggest challenge the Red Cross faces is the cost of the actual service they provide. It's one that is constantly increasing in cost and maintaining and achieving adequate funding to be able to do the services they do is a challenge for them. However, they manage it to a pretty good level and as an Australian and a blood donor I would encourage anyone who has an opportunity who can donate blood to do so as it is a very worthwhile cause.

The Red Cross also acts as the centre of transfusion expertise in the country. The transfusion medicine specialists who work in the Red Cross provide clinical expertise to other doctors and so on and advise them about the best way to treat their patients with these blood products and they act as the centre of expertise is you like.

Another function the Red Cross has is to manage, produce and distribute fresh products. Those are products like fresh frozen plasma used in certain indications for platelets, for coagulation disorders, red cells, etc. These are products that don't require refractionation so the Red Cross take the donations given to them, produce these products and then distribute them. What they don't have the capability of doing is the actual process of refractionation which is what we do with the plasma. That needs to go to a specialist company or a specialist business that can fractionate it, which is basically a manufacturing process to turn it into the finished products we see as IVIG and so on.

In Australia we have had the fortunate situation for a long time of having the Commonwealth Serum Laboratories (or C.S.L as it was originally known) providing fractionation services for Australia. While it was actually a Government authority originally, it was privatised back in the early 90's and it is now a commercial company just like Octapharma is and many other companies around the world who specialise in these types of services. Something to bear in mind is that the Red Cross collection of blood is done under a voluntary system which is funded through the Government. The fractionation process is actually done by private industry and that's done under a contract again with the Government and it's something to bear in mind.

Australia has what we would call probably one of the best blood systems in the world but it is not the only blood system and around the globe in many developed countries the way blood is collected, processed and then returned back to patients is very similar. Many countries have similar collection agencies like the German Red Cross and the Swedish Red Cross, the Swiss Red Cross and so on who act as similar agencies as the Australian Red Cross do. There is, however, in some countries a more physical presence of the commercial side of collection of blood, which we don't have currently here in Australia and one which would probably be unlikely to appear in Australia.

This is the case where the industry actually owns or manages the collection of blood as well as the processing of the blood and that's done under a commercial or business arrangement. CSL for instance is the largest commercial fractionator or commercial blood processor in the world and not only fractionates the plasma but also owns collection centres that collect the plasma in various countries. And that's normal for some fractionators. I should also mention that whether you are in Australia or in Europe or in the United States or Canada, the blood industry or the blood sector is probably the most stringently controlled, the most heavily regulated, the most scutinized industry of all industries and that's significant, because blood needs to be a good and secure product, needs to be ensured that the quality and the safety of the products are guaranteed to the recipients of the products and that's critical and the only way you can do that is through very stringent regulation and control.

In Australia we have an agency called the Therapeutic Goods Agency (TGA) and they have a blood section, a whole department that is specifically mandated with regulating and controlling the blood sector and the blood products in this country. In Europe the FGA drug administration has a similar department that controls and regulates bloods in their country. In Europe there is the European medicinal evaluation agency which does the same functions. These Agencies talk to each other and compare notes on a regular basis and meet on a regular basis internationally so they can ensure that the

products that are produced in say Europe and North America meet the same standards as those which would be produced in Australia. Products coming into Australia like any other pharmaceutical product you have for say hypertension or a heart condition they are regulated and controlled and registered products, blood products are no different they have to go through an evaluation process, a registration process and an approval process to ensure they are safe to be used in this country and the TGA guarantees and insures that process and they are the government agency that is responsible for that process.

Because the blood industry as a commercial business and is so heavily strutinized and controlled by government, it is very difficult for companies to commence operations in this business or indeed to in some situations to maintain a viable business in the industry, so a lot of people have seen the number of companies in the global business decrease and there has been a lot of consolidation in the industry that has meant there is maybe 10 large multi-national companies around the world that specialise in providing blood products to a global market. CSL is the largest, Baxter is another company which is a US based company, Octapharma is another company which I represent and there are a number of companies around the world that now supply the world on a global basis and the market is considered a global market rather than just individual countries.

So in Australia we have a number of stake holders or players. We have the Australian Government as the funder and the regulator of the industry. We have the National Blood Authority which is the peak body for the management for the blood industry of Australia. We have the regulator who is the T.G.A. who I have talked about and we have the Australian Red Cross which provides the collection and distribution of the blood products that we've talked about and then we have the commercial part, the refractionation side of the industry. In Australia we have CSL as the national fractionator and then we have other companies that are involved in the industry and have come to Australia.

I would like to emphasize the importance of the IVIG as a component of the fractionation of blood. It is probably the most significant and the most important part of the fractionation of blood or plasma. The role of IVIG is crucial in the management of many many diseases and many many conditions. As a result the demand for these products continues to grow. So we have to ensure that we use the available resources of blood effectively and efficiently the best way we can.

At Octapharma we state that our motto if you like is for the safe and optimal use of plasma globally so we are striving for on a daily basis to ensure we get the highest quality products, the safest products available if possible and to use the plasma we do have available in the best and most efficient way we can.

IVIG use in Australia. We have been self sufficient here in Australia for blood products and IVIG for many years, however, with the increasing demand for IVIG treatment it became more and more difficult and more and more of a challenge to try and manage the supply and the demand for the finished products. As I mentioned earlier the Red Cross has an ongoing challenge to try to collect enough blood and plasma to supply CSL to fractionate to turn into finished products so they can send

back to the patients. When they can't get enough plasma to send to CSL unfortunately we have had situations where there has been shortages and I'm sure you are all familiar with what's occurred in the last few years; certainly in 2002/2003 where there were chronic shortages and patients with certain conditions were actually unfortunately having to be scaled back on their treatment with obviously not having enough IVIG to manage their conditions well.

There has been for a long time some other imported product that has been brought into the country on an ad hoc basis and one of them was Sandoglobbulin which has been imported since 1987. So there has been some attempts to shore up the supply of IVIG in Australia and to try and guarantee or ensure that there is enough to supply the requirements of the patients. The Government has recognised this for a long time and there have been a number of reviews of the blood sector and the plasma industry starting back in '95 with the **** Ca??? report*** and then the Stephens Review and the Australian Health Ministers' Advisory Council also participated in a review specifically on IVIG back in 2000. All these governmental reviews were designed to try and ensure the security of supply and adequate supply enough to ensure that there was enough product available. Prior to 2003 the Blood Sector was a little bit fragmented based on States. The Red Cross in each State managed the agreements for their state in terms of their agreement with CSL for the fractionation of their state's product and it wasn't until probably 2001/2002 where it was actually brought into a national system where it was under a national umbrella and the Red Cross became a national organisation with national distribution targets and supply targets and so on. The National Blood Authority was actually only created in 2003 so it's a relative new system here in Australia of having a national approach where each state is not just responsible for refractions of their own requirements of their own products but it's managed on an Australian wide basis.

In 2003/2004 the National Blood Authority looked very hard at how they could ensure there would be enough products available for all patients and one of the things they did was to address supply issues of IVIG for contingent supply where they put a tender out if you like for the supply of an alternative produced product to ensure they would never run out again. CSL supplies an imported product Sandoglobbulin under that agreement and Octapharma supplies a product Octagam under that agreement as well.

There are a number of products now being used in Australia. When there is only one Brand out their or one product that is being supplied people tend to think or assume that thats the only product available and IVIG is just one product. While that's not quite the case there is a number of products out there and if you look around the world there is more than 30 to 40 different brands and each of those brands are different in different ways. They are manufactured differently; they have different product specifications so the way they are manufactured is different. So we can't assume that one IVIG is exactly the same as the next so there is some differences and this is something to be aware of all these small differences do effect things like safety, how the patient responds to the treatment which is called efficacy, how well the patient can tolerate it that's tolerability and how it's to be used convenience and obviously with the different production processes some of the products have different costs implications so we just can't assume that IVIG is the same and one product is exactly

the same. We can't assume that we have got to appreciate there are differences and be aware of them.

That leads me to the next part of the talk I guess and that is "Who is Octapharm and What is Octagam? 'Octagam' is our IVIG just as CSL manufactures and supplies their IVIG called 'Intragam'. Often when patients are being treated with IVIG they say "I'm being treated with 'Intragam'. They assume that it is 'Intragam', where in fact they could be receiving quite a different quality not being quite aware that it is actually a different brand. Hopefully people will be now aware that there are different brands out there and they may have slightly different characteristics. However, Who is Octapharm and what do we do? We are in fact the largest independant plasma company in the world. We are a privately owned company which is quite different to most of the other multi national plasma or blood fractionation companies.

CSL is listed on the Australian Stock Exchange and you can actually go and buy shares in their company and their division CSL Bioplasma is the division of that CSL company that produces and acts as a commercial manufacturer of IVIG.

Octapharma is a privately company owned by the Mardeer family of Switzerland and it was established in 1982. It has had more than a 20 year focus on IVIG products and this is all they do. They don't have other divisions that do things like vaccines, other pharmaceuticals, medical devices or what have you, they only specialise in blood and fractionated blood products specifically. They actually have an implication because to be able to buy in to the industry you have to be very very good at what you do as, as I have indicated earlier, the regulations and scrutiny and the demands of government control around the world necessitates companies being highly ethical and very efficient at what they do to ensure they can provide safe, quality medications.

Octapharma as I have said is a private company based in Switzerland but they are a multi national company as we have manufacturing facilities in five countries in Europe. Three of those facilities are actually licensed to produce Australian product or product for Australian distribution. That is important, because you can't just produce a product in any country and supply it to Australia unless it has been approved and registered to do so. So there is a long process of going through the TGA (Therapeutic Goods Association) to evaluate and ensure the product meets the requirements of the Australian Government, are safe and of enough high quality to ensure they won't cause problems to the patients who receive them. So Octapharma went through a long process of registering and gaining approval to market their products in Australia and we now have a number of products that are registered and can be sold here which ensures that the product is acceptable to Australia and there is no problems of safety, etc. as that is all controlled by the Government.

We are an international company. We operate in more than 70 countries around the world and we have a heavy or very strong focus specifically on blood products. This is all we do - blood plasma. This is the future of the organisation. We can't rest on our laurels and just say "well this is today's product and we are not to do anything for the future". We need to constantly research and development new technologies and new products for the future as this is what our company depends on. We put a large amount of money back into research and development.

In 2004 Octapharma commenced Australian operations. They opened an office in Sydney as their Australian headquarters and since 2005 have been supplying 'Octagam' under the standing offer of contingent supply agreement with the National Blood Authority. We also sell our product on the private market as well to hospitals which is a smaller section of the business but an important one as well, because the government will only pay for usage in some indications and some indications aren't reimbursed by the government so some patients, some hospitals will purchase the product to be used in what we call a private or jurisdictional drug order situation.

Octapharma came to Australia to set up operations with a long term view for participating in the Australian industry. We are not just here to supply the shortfall in current supply requirements, we are actually here to participate fully within the health care system and everything we do is designed to establish our presence here in Australia.

We have a range of products. IVIG is just one of them. They are across a whole range of areas where blood products can be used.

Which leads us to 'Octagam'.

Its an IVIG – that's what it looks like. It looks extremely similar to a bottle of 'Intragam' but with different labels. (One of our members interjected with – Do you have any free samples?) It's a liquid. It is used in a very similar way. It's administered through an intravenous line. It is very similar and if you were provided 'Octagam' instead of the 'Intragam' product you shouldn't be too concerned because they are very similar. However, there are some characteristic differences that you should be aware of or your doctor should be aware of, so that if there are issues or considerations that need specific management they can look after that, but from a recipient or patient point of view you shouldn't notice much difference when you receive our blood product or the other product.

Question: "The actual amount in solution – is that the same." **Answer:** " Do the products have slightly different concentrations? The 'Intragam' product is a 6% concentration and the 'Octagam' product is a 5% concentration. It does mean that there is a small variation. Our bottles contain 2.5g, 5g or 10 g. The CSL contains 3, 6 and 12 g. However the dosage from the doctors' point of view is exactly the same. Therefore if you are prescribed 40g of IVIG per dose or treatment it would be the same for 'Octogam' or 'Intragam'. The only difference would be the number or range of bottles that the hospital would give you to be infused.

Question: Relating to your first slide it take 300-350 donors to get 10g of Octagam which I think your presentation said would be a dose for a CIDP sufferer. If a CIDP sufferer gets 30g of Intragam does that mean that 900 – 1000 donors would be needed? **Answer:** Yes . The amount of blood donations that go into producing IVIG regardless of which manufacturer is making it is probably comparable. Differences are because the concentration of the immunoglobulin molecule that you try to extract is similar. It is 1-3% of the blood product. The difference would be in how big their pool size is in terms of their manufacturing process. Some companies use quite a large pool size of let's say 10,000 litres at a time which means that the number of donations that go into that pool is huge. Other companies like Octapharma

produce their batches on a much smaller pool size of 3500 litres which is one third of the pool size so the number of donors that are contributing is slightly smaller. It comes down to how many donors are required to make the finished product and I think the rule is 300 – 350 donors per 10 grams.

When there is a shortage of 'Intragam' and in some certain indications of management the Red Cross who acts as the allocatur, distributor and controller of the blood products makes the decision as to which produce is allocated to the patient. They try and keep the patient on the same product as long as they can and they try not to switch patients. Unfortunately sometimes because of the supply system they can't supply the same product and they do require the patient to change. They don't like to do it, and it's not clinically good practise to do it but sometimes they have to. It is part of the Red Cross' role to manage that as best they can.

Question: When it first came out, the problem with the shortage of 'Intragam', I thought there was some problem with some of these replacements being synthetic to a certain extent and that was the problem switching from one to another.

Answer: IVIG is currently produced synthetically. It is all produced in a very similar way. The starting material is the same which is the plasma. The way it is manufactured can change a little bit and the specification at the end is a little bit different and some products are not liquid, some product are what they call ……genised or powdered like Sandoglobbulin for instance. That's a powder product and to be able to use that the nurse has to reconstitute that back to a solution to infuse that, no you can't use a synthetic. It needs to be produced from the original blood.

The nurse said it is very similar. It comes down to the constituents which are generally the same. The percentage of the constituents might alter. For instance some of the IVIG brands have higher levels of iga or lower levels of iga. Now iga has a specific role to play in immunoglobulins and certain patients can't receive products that have high levels of iga and that's a consideration, so the recipe that the manufacturers use and the way they produce the product does result in slightly different variations but essentially they are the same. They all have similar igg protein subclass distribution with subclass molecules that are very similar but they might be in different quantities. This is the reason why we presented to you, if all products were the same then there would be no issue but all brands are slightly different by a little bit which does mean they have different specification which does mean that some patients respond differently but overall they are similar and they are close enough to the same, so you can substitute them quite easily so you can use one brand or the other brand but there are supple differences which do make a little difference.

Is their no synthetic product on the horizon. Not that I'm aware of. Unfortunately the protein molecule the ig molecule we extract to make this product can't be replicated in a synthetic. What they are trying to do is increase the efficiency and the ability to extract more of the protein molecules from the existing plasma and this is what we call high yield IVIG as the amount of finished produce from the raw starting material does have an impact on how much you can supply and that is an important consideration so there are a lot of ongoing development and research particulary around IVIG but I'm not aware of any research to try and make a synthetic.

Statement by member John Burke. The synthetic furfy got around the lay circles when Sandoglobbulin came in because it was in a dry form and had to be reconstituted so it was people were of the opinion that it was a synthetic product.

Strength of 'Octagam'. The concentration within the actual liquid is the only difference. The dosage for it to be clinically effective is exactly the same. If you require 30 or 40 grams your dose is the same, just the volume you receive by infusion may be slightly different. The same amount of ig component in that produce will be the same.

Question: Is there a difference in the speed that products can be infused?
Answer: There is. Different products have different speeds of infusion and that's because different products if you infuse them faster can't be as well tolerated so there a relationship with tolerability to the speed it can be infused at. Also it goes back to when the product was being researched and developed and what protocols the companies used to determine their rate of administration and that depended on what they registered for approval for the product to be used commercially, they had to use that research base for their application therefore if they had used a certain speed of infusion during their research and development phase that's the rate that would be approved for their patients.

'Intragam', the maximum rate of infusion that they recommend is 245 mls. per hour. 'Octagam's maximum recommended rate is calculated slightly differently. The 'Intragam' product is based on a mls. per hour basis. Our product is calculated on the weight of the patient, so it's weight dependant and we have an indication which is a licence to administer 5 mls per kilo per hour with a maximum recommended rate of up to 480 mls. in any given hour, so potentially a heavier weighted person could be infused a little faster. It's just on the licensing of the product that determines how fast it can be administered.

There is usually a correlation between the tolerability or how well patients can tolerate the product and the speed of the infusion. Some products have a quite slow administration rate because they are not as well tolerated and people have more reactions to them.

Question: My infusions are at 120mls. per hour. What is the reason for this?
Answer: All rates of infusion are recommended rates up to a maximum rate and it is always up to the physician or the nurse that is doing the administration as to what the rate of infusion is, so there may well be a reason why the nurse or doctor has recommended that you have a rate of 120 mls.