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Biological Science Section
Office of Scientific Evaluation
Therapeutic Goods Administration
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Dear Sir or Madam,

Novartis Comments: Regulation of autologous stem cell therapies: Discussion paper for consultation

Novartis Pharmaceuticals Australia Pty Ltd ("Novartis") welcomes the opportunity to provide written comments based upon its review of the Therapeutic Goods Administration's (TGA) Discussion paper requesting consultation on the regulation of autologous stem cell therapies. In so doing, it is not our intent to answer each and every question posed by TGA in the discussion paper but rather address key points that we believe strike at the heart of our concerns regarding the current state of affairs of the emerging and rapidly growing autologous stem cell therapies market in Australia which is not currently regulated under the *Therapeutic Goods Act, 1989* ('the Act'). Our comments echo concerns expressed in some recent publications, which call for greater regulatory oversight to protect vulnerable patients and that at this time, the provision of unproven stem cell therapies outside of clinical trials is unethical[1, 2].

Novartis Recommendation

Novartis recommends that Option 5 be adopted and further developed by TGA to ensure the safe and effective use of autologous stem cell therapies. ***Discussion***

In the request for comment, TGA created the heading of **"Does the current regulatory model for stem cells need to change?"** TGA lists the following concerns in the discussion paper which have been expressed to the Agency in various public forums. Novartis will discuss its recommendation in the context of each of these concerns.

Safety of the products – either direct safety impacts of safety issues incidental to the therapy

There is a perception that use of minimally manipulated autologous stem cell therapies carry no or minimal risk since the stem cells are harvested from the donor-patient, undergo minimal ex vivo processing or manipulation prior to their reintroduction into the same donor-patient often within hours of their original harvest. One of the most common autologous stem cell therapies currently accessible to patients is the use of stromal stem cells isolated from adipose tissue harvested by a liposuction procedure and intended to treat osteoarthritis.

Complications may arise from standard liposuction procedures, the most notable being localized infections due to contamination occurring during the harvest procedure. Some infections may become more serious leading to necrotizing fasciitis and or toxic shock syndrome. Embolism of fat droplets loosened during harvest and entering

the circulatory system and lodging in pulmonary tissue, seroma formation, skin necrosis, toxic effects of local anesthetics and deaths have all been reported in association with liposuction procedures.[3] See also Attachment 2 of the discussion paper.

Post-harvest contamination of the stem cell product during cell processing steps and prior to re-infusion back into the patient is also of concern raising the need for stem cell clinics to put in place good manufacturing practices to assure the quality and purity of the product in order to protect the safety of the patient. One must also be concerned about the traceability of patient stem cell lots as they undergo ex vivo processing at a stem cell clinic. Conceivably, high volume clinics may perform procedures on multiple patients during a given work day with the potential risk that a patient may accidentally receive cells sourced from another patient thus turning an intended autologous procedure into an allogeneic stem cell transplantation which would have potential near and long-term safety concerns. These concerns can best be addressed by mandatory registration of cell processing facilities to assure established and accepted manufacturing, quality control standards and adequate employee training are all in place to minimize the risk of product contamination and assure traceability and identity of stem cell aliquots through ex vivo processing period and re-infusion/injection into the correct patient.

The route of delivery of the finished therapeutic product is also of concern since there are also inherent risks associated with intravenous infusion of cell suspensions or the intra-articular injections when used for the treatment of osteoarthritis. Any physician and facility administering stem cell product should be adequately trained to assure the safe and proper delivery of the finished product in its intended manner of use and be prepared and equipped to handle any serious and life threatening adverse reactions which might occur in an acute setting such as infusion reactions and pulmonary emboli following intravenous infusion of cell suspensions.

The point to be driven home is that there are risks associated with all medical procedures and this is of particular concern in the setting of unregulated autologous stem cell therapy where mandatory safety reporting is currently not required.

Lack of evidence to support the efficacy of the products

Despite being an intrusive procedure with many high-risk steps, establishing the efficacy of autologous stem cell therapy is currently not required prior to their widespread use in Australia. Lacking efficacy data generated from adequately designed controlled clinical trials, such therapies offer no established benefit and therefore are only associated with known risks which leads us to conclude their unregulated use cannot be supported. This is of particular concern in instances where established, cost-effective approved treatment options may be available for some of the conditions that are being targeted for autologous stem cell therapies.

The large sums of money being charged for unproven treatments

It is our position that routine and widespread use of unproven medical treatments cannot be condoned regardless of the sums charged.

Lack of mechanisms for reporting of adverse effects of the products

This is a major concern especially when taken in tandem with no requirement for any evidence to demonstrate the efficacy of these products. In the discussion paper, TGA summarized its own efforts to gather safety related background information regarding the use of autologous stem cell therapies (Attachment 2 of the discussion paper). TGA concluded that no significant safety issues pertaining to therapeutic use of mesenchymal and/or adipose derived stromal cells were identified based upon published literature but offered that the absence of

reporting requirements poses limitations on the ability to draw firm conclusions on the relative risks or safety of these products.

Therefore, Novartis would support a requirement for stem cell clinics to track and report adverse effects as required for biologic products which are licensed under the Act. This is one way to gain a better handle on the overall safety of such therapies when widely used by a diverse group of medical practitioners with varying levels of medical specialty training in real-world settings.

Inappropriate advertising of the products

Information regarding available stem cell therapies in Australia which are directed towards the general public can be readily found on the internet. These sites generally offer very little evidence to substantiate their medical product claims often relying on patient testimonial in the form of video clips professing to the simplicity, affordability and immediate beneficial affects their stem cell procedure had in improving their condition and overall quality of life.

It was also noted that these clinic websites often add a standard disclaimer informing potential patients that individual results may vary instead of providing facts on the number of procedures performed with objective measures to assess levels of success and therapeutic failures as well as the types and frequencies of side effects related to such therapies. Many of the conditions targeted for treatment by stem cell clinics are of a chronic nature often effecting the elderly population who are more prone not to question the veracity of testimonial forms of promotion. Therefore, it is recommended that promotional advertising be limited to physician directed messaging and required to provide sufficient information with respect to scientific evidence to support the intended use of a product for a specific indication as well as summarizing important key safety information.

Additional comments

The US FDA has recently issued two related draft guidance documents; *(draft) Guidance for Industry: Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products* (December 2014)[4] and *(draft) Guidance for Industry: Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations* (December 2014)[5] which provide answers to common questions regarding the determination of minimal manipulation and homologous use. Particular attention is called to the Adipose Tissue document which considers adipose tissue a form of connective tissue which serves as an energy store for lipids, insulates the body and provides cushioning to support subcutaneous tissues and internal organs. The collection and isolation of stromal stem cells from adipose tissue for clinical therapeutic uses would be considered more than minimal manipulation and use of adipose tissue to treat bone and joint diseases would be considered non-homologous use.

We raise this to TGA's attention because many of the autologous stem cell clinics now operating in Australia seem to be directed towards the treatment of joint and tendon conditions with stromal stem cells derived from adipose tissue. Application of similar classification criteria in Australia as proposed by the US FDA would require many of these stem cell therapies to be regulated under the existing Class 2, 3 or 4 Biologics framework and require evidence of safety and efficacy for inclusion in the Australian Register of Therapeutic Goods (ARTG). Requiring proof of efficacy and safety of specific therapies will permit an objective assessment of whether an acceptable risk/benefit profile has been established to allow for widespread use of such products, thus protecting the health and safety of individual patients as well as the overall population.

Overall Conclusion

Novartis recommends that TGA adopt option 5 for the regulation of autologous stem cell therapies. This option will provide the highest level of patient safety and create the best opportunity to ensure that patients are

receiving complete and accurate information about the therapies that are being offered to them in medical clinics. This level of regulation would be consistent with requirements in other jurisdictions and commensurate with the potential benefits and risks. Importantly, it could be regulated under the TGA's existing biological framework thus avoiding duplication of regulatory processes or creating an unnecessary additional burden.

Novartis thanks the TGA for considering this submission and would be happy to expand on any part of it.

Yours sincerely,

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1. McLean AK, Stewart, C and Kerridge, I. Untested, unproven, and unethical: the promotion and provision of autologous stem cell therapies in Australia. Stem Cell Res Ther. 2015; 6(1): 12. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4327954/
2. McLean AK, Stewart, C and Kerridge, The emergence and popularisation of autologous somatic cellular therapies in Australia: Therapeutic innovation or regulatory failure? JLM 22: 65-89 http://ses.library.usyd.edu.au/bitstream/2123/12282/2/JLM-the-emergence-and-populatisation-2014.pdf
3. US Food & Drug Administration (2015). Liposuction: What are the risks and complications (as accessed on 23-Feb-2015) http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/Liposuction/ucm256139.htm
4. US Food & Drug Administration (2014). (draft) Guidance for Industry: Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (as accessed 23-Feb-2015). http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm427692.htm
5. US Food & Drug Administration (2014). (draft) Guidance for Industry: Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) from Adipose Tissue: Regulatory Considerations (as accessed 23-Feb-2015). http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm427795.htm