Sharon
BIO-MEDICINE LTD.
ISO 9001 - 2008 Certified Company

09 Aug, 2018

To whom it may concern,

Elemental Impurities Statement- Nifedipine

ICH Q3D Guideline: "Impurities: Guideline for Metal Impurities" was published with implementation dates in the EU regions of June 2016 for new marketing authorization applications and December 2017 for all existing products on EU market. The guide was endorsed by Japan MOH as well and US FDA.

USP general chapter <232> "Elemental impurities - Limits" and USP <233> "Elemental Impurities -Procedure "are expected to become effective on January 1, 2018.

As per ICH and USP directives, Nifedipine manufactured by Sharon Bio-Medicine Ltd, API Unit-II, site was subjected to a risk assessment protocol that covers all potential sources of metal contamination such as water, air System, manufacturing process, production equipment and evaluation of raw materials used in the route of synthesis of the API and the potential risk from the API primary packaging materials.

Sharon Bio-Medicine Ltd. hereby declare that no metals are used in the manufacturing process of Nifedipine.

In relation to the elemental impurities potentially present even when not intentionally added, Nifedipine is intended for tropical, oral administration and consequently, class 1 and class 2A elements are considered for analysis of three batches of the API for metal residues. The results were obtained by a validated method and are considered accurate.

All metals residues were found to be below the Control threshold (30% of PDE) calculated levels values assuming 0.03g/ day daily dose of the final API per their administration route.

The outcome of the thorough risk assessment indicated that there is no risk for metal contamination originated from the API.

As such, no change of the manufacturing process of the API and no further controls on elemental impurities are deemed necessary.

Any future change made to the API process will be subjected to rigorous change control process that will evaluate the potential impact on the above conclusion.

The Risk Assessment Summary and 3 lot results obtained is enclosed in **Appendix 1**

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Appendix 1: The Risk Assessment Summary

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Nifedipine is intended for oral administration and consequently, class 1 and class 2A elements are considered for risk analysis.

Elements	Oral PDE (µg/Day)	Therapeutic daily Dose (TDD)(gm)	Control threshold (30% of PDE)	Batch Analysis Results (ppm)		
				SBML/NFD/17002	SBML/NFD/17004	SBML/NFD/17005
Cd	5	0.03	1.5	Absent	Absent	0.04
Pb	5	0.03	1.5	Absent	Absent	Absent
As	15	0.03	4.5	Absent	Absent	Absent
Hg	30	0.03	9.0	Absent	Absent	Absent
Co	50	0.03	15.0	Absent	Absent	Absent
V	100	0.03	30.0	Absent	Absent	Absent
Ni	200	0.03	60.0	Absent	Absent	Absent

API name and Intended route of administration: Nifedipine				
Elements	Class	Intentionally Added	Considered in Risk	Conclusion
Cd	1	No	Yes	Results of each elements are less than the Control threshold (30%of PDE) hence no further controls required.
Pb	1	No	Yes	
As	1	No	Yes	
Hg	1	No	Yes	
Co	2A	No	Yes	
V	2A	No	Yes	
Ni	2A	No	Yes	

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