P.5.5 – Characterization of Impurities

Reference is made to 3.2.S.3.2 (Impurities) for details on organic impurities observed in the drug substance.

1. Elemental Impurities

No elemental impurities are intentionally added during the manufacturing of drug product. An elemental impurity risk assessment for stelbatalol has been conducted, taking all risk factors into account, in accordance with ICH Q3D. This risk assessment focused on the potential presence of elemental impurities introduced by the drug product components, manufacturing process, and packaging materials.

Representative batches of stelbatalol drug product were tested for the four Class 1 elemental impurities Cd, Pb, As, and Hg; the three Class 2A elemental impurities Co, V, and Ni; and Class 3 elemental impurity Cu intentionally added in stelbatalol drug substance manufacturing. Elemental impurity results summarized in the table below meet the ICH Q3D requirements based on a maximum daily intake of 20 mg of drug product.

P.5.5 Characterization of Impurities

Table 1. Elemental Impurity Results for Stelbat Drug Product

Batch Number	Strength (mg)	Manufacturing Site[a]	Class 1				Class 2A			Class 3
			Cd (ppm)	Pb (ppm)	As (ppm)	Hg (ppm)	Co (ppm)	V (ppm)	Ni (ppm)	Cu (ppm)
33445	20 mg	AAA Pharma (NJ, USA)	< 5	ND*	< 10	ND*	< 50	< 10	ND*	250
33446	20 mg	AAA Pharma (NJ, USA)	ND*	ND*	< 10	< 10	< 50	< 10	ND*	223
33447	20 mg	AAA Pharma (NJ, USA)	ND*	ND*	< 5	ND*	< 50	< 10	ND*	199

*ND, not detected

P.5.5 Characterization of Impurities

2. Presence or Formation of Nitrosamine Impurities

No nitrosamine impurities are intentionally added in the manufacture of Stelbat drug product. A nitrosamine risk assessment has been conducted, taking all risk factors into account in accordance with principles from ICH Q9 and M7. This risk assessment focused on the potential for nitrosamines to form or be introduced to the drug product and its manufacturing process.

Potential contamination of the drug product was assessed by first identifying possible nitrosating agents present in the process from the raw materials and drug substance. Further assessment was performed for adventitious nitrosating agents, including potential reaction with low levels of nitrite that may be present in process water. When nitrosating agents may be present, the manufacturing process as well as primary packaging components were assessed for the presence of secondary or tertiary amines that may react to produce N-nitrosamines. The manufacturing process was assessed for the risk of cross-contamination of either of these species by facilities, cleaning, or recycling/reuse of materials including solvents. No materials are recycled or reused in the drug product manufacturing and cleaning processes.

When there was the possibility of a nitrosating agent and reactive amine being present in a manufacturing step, an analysis of the process was conducted to determine potential levels of these impurities. Following this assessment, it was concluded that there is no risk identified for the presence of nitrosamines in the drug product.

None of the excipients used to manufacture Stelbat have amines or nitrosating groups in their structures. Of the excipients used, only the magnesium stearate and maize starch have the potential for presence of nitrosating agents, such as nitrite. The magnesium stearate has not more than 0.53 ppm nitrite, as tested by the supplier, whereas the maize starch was found to contain < 0.2 ppm nitrite content.

In conclusion, no significant risk of nitrosamine impurities has been identified for the drug product, supporting the position that no testing for nitrosamines is required.

1.1 Presence or Formation of Nitrosamine Impurities from Immediate Packaging and Printing Inks

Two packaging configurations are being evaluated for use with Stelbat: bottles with screw caps and blister packs.

Stelbat drug product is packed in white, opaque bottles constructed of white high-density polyethylene (HDPE) resin. The bottles are closed with a 10 mm polypropylene two-piece, child-resistant closure that includes a pulp liner and aluminum foil induction seal. The induction seal consists of foil, polyester and polyethylene (in contact with the product prior to opening). The bottle and container closure components

have no identified source of nitrosating agent or secondary/tertiary amine and thereby present no risk of forming nitrosamine impurities.

The Stelbat drug product blister packaging uses Polyvinyl Chloride (PVC) Aclar laminate film layer blisters sealed with 10 μm push-through hard temper aluminum foil lidding.

Negligible risk of nitrosamine formation is expected from the blister packaging material based on the chemical structures of the components. PVC ($(C_2H_3Cl)_n$) does not contain nitrosating agents or secondary and tertiary amines. Based on material inputs to the blistering process, there are no sources of nitrosating agents to react with any reactive amine to form nitrosamines. Therefore, formation of nitrosamines in the blister film is not expected, as there are no intentionally added reagents or chemistries that generate nitrosamines.

Therefore, the risk of nitrosamines from primary packaging components impacting the drug product is negligible and there is no risk to patient safety.