**Drug substance:** AZD4635 ( Imaradenant )

**Route of administration:** Oral

* AZD4635 is an orally bioavailable antagonist of the adenosine A2A receptor with potential immunomodulating and antineoplastic activities
* AZD4635 selectively binds to and inhibits A2AR expressed on T-lymphocytes
* This blocks tumor-released adenosine from interacting with A2AR and prevents the adenosine/A2AR-mediated inhibition of T-lymphocytes.

**Molecular Structure**:



**Formula:**  C15H11ClFN5

**IUPAC :** 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine

**Storage/Stability :**

* 3 years , -20°C, powder
* 2 years, -80°C, in solvent

**HPLC**: 99.17% purity

**Solubility**:

DMSO - 63 mg/mL (199.53 mM)

Water solubility - < 1 mg/mL

Ethanol - 4 mg/mL (12.66 mM)

**Qualification and Identification thresholds :**

**100 mg/day (MDD) :**

 1 mg/day

Qualification Threshold 100 mg/day dose (%) : = ----------------- \* 100 = 1 %

 100 mg/day

Identification Threshold is 1 %

**200 mg/day (MDD) :**

 1 mg/day

Qualification Threshold 200 mg/day dose (%) : = ----------------- \* 100 = 0.5 %

 200 mg/day

Identification Threshold is 0.1 %

**1000 mg/day (MDD) :**

 1 mg/day

Qualification Threshold 1000 mg/day dose (%) : = ----------------- \* 100 = 0.1 %

 1000 mg/day

Identification Threshold is 0.05 %

**1500 mg/day (MDD) :**

 1 mg/day

Qualification Threshold 1000 mg/day dose (%) : = ----------------- \* 100 = 0.06 %

 1500 mg/day

Identification Threshold is 0.05 %

|  |  |  |
| --- | --- | --- |
| **MDD** | **Qualification threshold (%)** | **Identification threshold (%)** |
| 100 mg/day | 1 | 1 |
| 200 mg/day | 0.5 | 0.1 |
| 1000 mg/day | 0.1 | 0.05 |
| 1500 mg/day | 0.16 | 0.05 |

**Metals and Impurities :**



**Palladium (ppm) :**

PDE = 100 ug/day

Dose = 100 mg/day

Concentration - maximum allowable limit = 100 ug/ 0.1g = 1000 ppm

**Iridium(ppm):**

PDE = 100 ug/day

Dose = 100 mg/day

Concentration - maximum allowable limit = 100 ug/ 0.1g = 1000 ppm

**Pyridine:**

PDE = 2 mg/day

Dose = 100 mg/day

Concentration - maximum allowable limit = 2 mg/day / 100 mg/day = 2%

|  |  |  |  |
| --- | --- | --- | --- |
| **Impurity** | **PDE** | **Dose** | **Maximum allowable limit**  |
| Palladium | 100 ug/day | 100 mg/day | 1000 ppm |
| Iridium | 100 ug/day | 100 mg/day | 1000 ppm  |
| Pyridine | 2 mg/day | 100 mg/day | 2% |

**Solvents:**

**Methanol:**

PDE = 30 mg/day

Dose = 100 mg/day

Concentration - maximum allowable limit = 30 mg/day / 100 mg/day = 0.3%

**Tetrahydrofuran**

PDE = 7.2 mg/day

Dose = 100 mg/day

Maximum allowable limit = 7.2 mg/day / 100 mg/day \* 100 = 7.2 %

**DMSO - d6:**

PDE = 500 ppm (5 mg/day)

Dose = 100 mg/day

Maximum allowable limit = 5 mg/day / 100 mg/day \* 100 = 5 %

**Individual unspecified impurities**

Qualification threshold for 100 mg/day dose (%) = 1 mg/day / 100 mg/day \* 100 = 1 %

|  |  |  |  |
| --- | --- | --- | --- |
| **Solvent** | **PDE** | **Dose** | **Maximum allowable limit**  |
| Methanol | 30 mg/day | 100 mg/day | 0.3 % |
| Tetrahydrofuran | 7.2 mg/day | 100 mg/day | 7.2% |
| DMSO-d6 | 5 mg/day | 100 mg/day | 5 % |

**Batch Data (100 mg/day):**

**For Metals**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Batch # | Appearance | Color | Assay(%) | Identify by HPLC | Palladium(ppm) | Iridium (ppm) | Tantalum (ppm)< 1 | Water (%) |
| AZD4635\_A(Toxicology batch) | Powder | White | 99 | Complies | 98 | 29 | 0.7 | 0.5 |
| AZD4635\_B | Powder | White | 96 | Complies | 96 | 66 | 0.5 | 0.3 |
| AZD4635\_C | Powder | White | 97 | Complies | 67 | 69 | 0.4 | 0.4 |
| AZD4635\_D | Powder | Off-white | 94 | Complies | 60 | 69 | 0.3 | 0.2 |
| AZD4635\_E | Powder | White | 96 | Complies | 16 | 65 | 0.6 | 0.7 |

**For Impurities**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Batch # | Individual unspecified Impurities (%) | Total Impurities (%) | Tetrahydrofuran (%) | Pyridine (%) | Methanol (%) | Total volatiles (%) |
| AZD4635\_A(Toxicology batch) | 0.19 | 0.27 | 0.8 | 0.5 | 0.03 | 1.79 |
| AZD4635\_B | 0.17 | 0.25 | 0.3 | 0.6 | 0.06 | 1.38 |
| AZD4635\_C | 0.14 | 0.26 | 0.4 | 0.4 | 0.17 | 1.37 |
| AZD4635\_D | 0.15 | 0.25 | 0.5 | 0.5 | 0.08 | 1.48 |
| AZD4635\_E | 0.10 | 0.24 | 0.3 | 0.2 | 0.15 | 0.99 |

**Drug Substance Specification (**AZD4635) **:**

|  |  |  |
| --- | --- | --- |
| **Test** | **Acceptance Criteria** | **Results** |
| Appearance | Powder | Powder |
| Color  | Off-White - White | White |
| Identity (HPLC) | Must be comparable to a standard spectrum run under same conditions | Complies |
| Assay (LC) | Quantitative NMR (QNMR) : Consistent with structureNLT 94% and NGT 99% | > 98 % |
| Palladium (ICP-MS) | NGT 100 ppm  | 16 - 98 ppm |
| Iridium  | NGT 100 ppm | 29 - 69 ppm |
| Tantalum  | NGT 1 % | 0.3 – 0.7 % |
| Water (KF) | NGT 1 % | 0.2 – 0.7 %  |
| Individual unspecified impurities | NGT 0.2% | 0.10 – 0.19% |
| Total impurities | NGT 1.0% | 0.24 – 0.27 |
| Methanol | NGT 1.0% | 0.03 – 0.17 |
| Pyridine | NGT 1.0% | 0.2 – 0.6 % |
| Total Volatiles (GC) | NGT 2.0% | 0.99 – 1.79% |
| Tetrahydrofuran | NGT 1.0% | 0.3 – 0.8% |
| Particle Size | Report Results | 5µm |

**Justification for Limits Chosen :**

* In the Synthesis it was mentioned that crystallization was done control palladium and iridium to within the specification 100 ppm. That I choose acceptance criteria as 100 PPM and limits from the batch as 16-98 ppm for palladium , 29-69 ppm for iridium.
* Color range is from the experimental methods conducted ranging from off-white power to white power.
* Particle size chosen based since 5 µm filter was used in crystallizing vessel.