

APPENDIX A

SANOFI-SYNTHELABO RECHERCHE

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Stability of Oxaliplatin Solution in the presence of dissolved sugars

Department : Pharmaceutical Sciences

Author(s) : Allison Miller

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SIGNATURES

This document was prepared and reviewed by the following and approved as acceptable.

| AUTHOR(S) | | |
|-----------------------|-------------|------------------|
| | <i>Date</i> | <i>Signature</i> |
| Name: A Miller | | |

| REVIEWER(S) | | |
|---|-------------|------------------|
| | <i>Date</i> | <i>Signature</i> |
| Name: Edward J Baker (Head of Development Group 1) | | |
| Name: Anita Groundwater (Head of Scientific Documentation) | | |

| APPROVAL | | |
|---|-------------|------------------|
| | <i>Date</i> | <i>Signature</i> |
| Name: Ross Blundell (Head or R & D Operations) | | |

| DISTRIBUTION AUTHORISATION | | |
|--|-------------|------------------|
| | <i>Date</i> | <i>Signature</i> |
| Name: P D Rose (Director of Pharmaceutical Sciences, Alnwick) | | |

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SUMMARY

The OPX2 code for this study is PRO0057.

Oxaliplatin is known to undergo oxidative degradation in aqueous solution. The addition of reducing sugars may act as an alternative route of oxidation in the system and therefore prevent or minimise oxidative degradation of oxaliplatin solution.

Stability studies of the reconstituted lyophilised product, which contains lactose, have not detected the impurities associated with the oxidative degradation of oxaliplatin. Hence, it has been postulated that the lactose molecule may form a loose structure ("cage") around the oxaliplatin preventing degradation. The addition of reducing sugars may also protect against oxidative degradation by offering an alternative oxidative pathway.

This study aims to determine if the addition of various reducing sugars (lactose, maltose and glucose) and a non reducing sugar (sucrose), at a concentration of 5% w/v, to aqueous solutions of oxaliplatin enhance the stability of the solution compared to the current aqueous oxaliplatin solution formulation (drug in water). Sucrose was included as a control to observe the effect of sugars independent of their ability to reduce. An aqueous 5 mg/mL oxaliplatin in water solution was also examined as a control for this study.

The solutions were analysed (assay and TCI) initially and then after 3 months storage at 25°C/60%RH and 40°C/75%RH. If a positive effect on stability was achieved, further studies would be initiated to optimise the sugar concentration and the data produced would be used to support a patent application.

The Total Chromatographic Impurity (TCI) levels for all of the oxaliplatin in sugar solutions investigated were between 2 - 3 times higher than the level obtained for oxaliplatin in water after 3 months at 40°C/75%RH.

Addition of sugars (reducing and non-reducing) does not enhance the stability of the current aqueous oxaliplatin solution formulation.

1. INTRODUCTION

Oxaliplatin is known to undergo oxidative degradation in aqueous solution. The addition of reducing sugars may act as an alternative route of oxidation in the system and therefore prevent or minimise oxidative degradation of oxaliplatin solution.

Stability studies of the reconstituted lyophilised product, which contains lactose, have not detected the impurities associated with the oxidative degradation of oxaliplatin. Hence, it has been postulated that the lactose molecule may form a loose structure ("cage") around the oxaliplatin preventing degradation. The addition of reducing sugars may also protect against oxidative degradation by offering an alternative oxidative pathway.

This study aims to determine if the addition of various reducing sugars, at a concentration of 5% w/v, to aqueous solutions of oxaliplatin enhance the stability of the solution compared to the current aqueous oxaliplatin solution formulation (drug in water). An aqueous 5 mg/mL oxaliplatin in water solution will also be examined as a control for this study.

The solutions will be analysed (assay and TCI) initially and then after 3 months storage at 25°C/60%RH and 40°C/75%RH.

If a positive effect on stability is achieved, further studies will be initiated to optimise the sugar concentration and the data produced will be used to support a patent application.

2. OBJECTIVE

To determine if the addition of reducing sugars to aqueous solutions of oxaliplatin enhance the chemical stability of the solution compared to the current aqueous oxaliplatin solution formulation (drug in water).

3. STUDY DESIGN

The study was completed as described in the "Experimental Protocol For Stability Of Oxaliplatin In The Presence Of Dissolved Sugars" (see Appendix 1), with the exception of the analysis of the samples at the 30 day timepoint. This analysis timepoint was extended to 3 months, to allow ASD to complete the analysis of the oxaliplatin solution primary stability batches on schedule as per the stability protocols for the oxaliplatin solution product.

4. MATERIALS AND EQUIPMENT

4.1 Materials

- a) Oxaliplatin – Prodstar Item no: D008387, Lot no: 99-02064
- b) Lactose monohydrate 200 mesh Ph Eur, NF – Prodstar Item no: A000722, Lot no: AR032172
- c) D-(+)-Glucose anhydrous – SigmaUltra (99.5%), Lot: 80K1014
- d) Maltose monohydrate – SigmaUltra (minimum 99%), Lot: 80K10101
- e) Sucrose – SigmaUltra (>99.5%), Lot: 51K0026
- f) Water for Injections Ph Eur, USP – Prodstar Item no: A002627, Lot no: AR034049
- g) PVDF 0.22µm filter media, Millipore, Durapore 47mm GVWP04700
- h) Disposable sterile plastic syringes
- i) Disposable sterile needles
- j) Disposable sterile 1.2 µm filters (Minisart)
- k) 16mL Schott Amphabel, tubular, type I, clear glass vial – Prodstar Item no: A001731, Lot no: AR017373
- l) West Flurotec, 19mm bromobutyl stopper with B2-40 coating – Prodstar Item no: A009258, lot no: AR020196
- m) Aluminium seals - 20mm flip-off cap, translucent in colour – Prodstar Item no: A005246, Lot no: AR016305

4.2 Equipment

- a) Mettler AT261 balance - P/N 41451
- b) Mettler AT460 balance - P/N 27329
- c) Jenway 3410 Electrochemistry Analyser - P/N 26474
- d) IKAMAG Magnetic/hotplate stirrer - P/N 41207
- e) Isolator - cabinet 19
- f) Class II cabinet - cabinet 20
- g) Schubert Crimper - P/N 26084

5. RESULTS

The 5 mg/mL oxaliplatin solution samples were analysed by ASD for assay and Total Chromatographic Impurities (TCI). Separate HPLC systems are used to measure the levels of the following impurities in the oxaliplatin solution product: -

- Oxalic acid.
- Diaquo DACH Platin, SR200028 and any unknown (Diaquo unspecified) impurities in the oxaliplatin solution product, detected using this HPLC method.
- SR200034 and any unknown (unspecified SR200034) impurities in the oxaliplatin solution product, detected using this HPLC method.

Diaquo DACH Platin, SR200028 and SR200034 are known impurities found in the oxaliplatin solution product. Hence, the toxicological effects of these impurities have been determined and acceptance limits have been identified for some of these impurities (i.e. Diaquo DACH Platin NMT 0.80% and SR200028 NMT 0.60%).

Any unknown impurities detected using either the Diaquo DACH Platin HPLC method (Diaquo unspecifieds) or using the SR200034 HPLC method (SR200034 unspecifieds) have an acceptance limit of LT 0.20% (for each impurity), and the total of all of the unspecified impurities must be NMT 1.0%.

The acceptance criteria, as defined in the experimental protocol (see Appendix 1) for the oxaliplatin test solutions, states that the analytical results should remain within the following specifications, which are related to the aqueous oxaliplatin solution product: -

- Assay – should remain within $\pm 5\%$ of initial value
- Total Chromatographic Impurities (TCI) – should be significantly better than the oxaliplatin in water control solution

The sugar control solutions (sugar in water) were used as blank solutions for the HPLC analysis.

Table (5.) 1 - Analysis Results After 3 Months at 25°C/60%RH and 40°C/75%RH

| 5 mg/mL Oxaliplatin in: | Timepoint | Assay (% of nominal) | Oxalic acid (% w/w) | Chromatographic Impurities | | | | | | |
|-------------------------------|---------------|----------------------------|------------------------|----------------------------|-----------|------------------------|-----------|--------------------------|-----------------------|------|
| | | | | Diaquo | SR200028 | Diaquo unspecifieds | SR200034 | SR200034 unspecifieds | Total unspecifieds | TCI |
| Water | Initial | 101.2 | 0.11 | 0.26 | 0.06 | ND < 0.02 | ND < 0.02 | ND < 0.02 | ND < 0.02 | 0.43 |
| | 3 mth @ 25/60 | 100.0 | 0.16 | 0.26 | 0.30 | None ≥ 0.05 | ND < 0.02 | None ≥ 0.02 | None ≥ 0.05 | 0.72 |
| | 3 mth @ 40/75 | 98.8 | 0.23 | 0.23 | 0.41 | 0.11 | ND < 0.02 | None ≥ 0.02 | 0.11 | 0.98 |
| Lactose | Initial | 100.6 | 0.12 | 0.18 | ND < 0.02 | D < 0.05 | D < 0.05 | ND < 0.02 | D < 0.05 | 0.30 |
| | 3 mth @ 25/60 | 98.6 | 0.17 | 0.16 | D < 0.05 | 0.11 | 0.13 | None ≥ 0.05 | 0.11 | 0.57 |
| | 3 mth @ 40/75 | 99.0 | 0.22 | 0.12 | ND < 0.02 | 1.04 | 0.43 | 0.35 | 1.39 | 2.16 |
| Glucose | Initial | 100.6 | 0.10 | 0.30 | D < 0.05 | ND < 0.02 | ND < 0.02 | ND < 0.02 | ND < 0.02 | 0.40 |
| | 3 mth @ 25/60 | 99.2 | 0.15 | 0.25 | 0.06 | 0.06 | 0.10 | None ≥ 0.02 | 0.06 | 0.62 |
| | 3 mth @ 40/75 | 99.4 | 0.21 | 0.12 | ND < 0.02 | 1.43 | 0.62 | 0.94 | 1.56 | 3.32 |
| Maltose | Initial | 101.0 | 0.11 | 0.30 | D < 0.05 | ND < 0.02 | ND < 0.02 | ND < 0.02 | ND < 0.02 | 0.41 |
| | 3 mth @ 25/60 | 98.8 | 0.18 | 0.34 | 0.11 | 0.06 | 0.07 | None ≥ 0.02 | 0.06 | 0.76 |
| | 3 mth @ 40/75 | 98.6 | 0.22 | 0.13 | D < 0.05 | 1.18 | 0.42 | 0.21 | 1.39 | 2.16 |
| Sucrose | Initial | 100.0 | 0.10 | 0.28 | D < 0.05 | ND < 0.02 | ND < 0.02 | ND < 0.02 | ND < 0.02 | 0.38 |
| | 3 mth @ 25/60 | 99.0 | 0.16 | 0.29 | 0.18 | 0.05 | D < 0.05 | None ≥ 0.02 | 0.05 | 0.68 |
| | 3 mth @ 40/75 | 97.8 | 0.23 | 0.14 | D < 0.05 | 1.10 | 0.42 | 0.20 | 1.30 | 2.09 |

Transcription checked :

Date:

The assay values for all of the oxaliplatin solutions do not change significantly from the initial values and all remain within $\pm 5\%$ of initial after 3 months at 25°C/60%RH and 40°C/75%RH.

The oxalic acid and Diaquo DACH Platin impurity levels for the oxaliplatin in sugar solutions are similar to the values obtained for oxaliplatin in water at all timepoints and storage conditions. These impurities also remain within their acceptance limits (i.e. oxalic acid NMT 0.35% and Diaquo DACH Platin NMT 0.80%) throughout the study.

The SR200028 impurity levels are lower in the oxaliplatin in sugar solutions compared to the values obtained for oxaliplatin in water at all timepoints and storage conditions.

The SR200034 impurity levels in each of the sugar solutions (except the 5 mg/mL oxaliplatin in sucrose solution) increase significantly after 3 months at 25°C/60%RH, with quantifiable levels of SR200034 being detected, compared to the 5 mg/mL oxaliplatin in water solution, in which no SR200034 impurity is detected. A further increase in the SR200034 impurity level is observed in all of the oxaliplatin in sugar solutions (including the sucrose solution), compared to the oxaliplatin in water solution after 3 months at 40°C/75%RH.

The level of all of the other impurities (Diaquo unspecifieds, SR200034 unspecifieds, and total unspecifieds) for the oxaliplatin in sugar solutions do not differ significantly compared to the oxaliplatin in water solution initially and then after 3 months at 25°C/60%RH. However, after 3 months at 40°C/75%RH the levels of these impurities are higher in the oxaliplatin in sugar solutions compared to oxaliplatin in water solution.

The Total Chromatographic Impurity (TCI) levels for the oxaliplatin in sugar solutions are between 2-3 times higher than the levels obtained for the oxaliplatin in water solution after 3 months at 40°C/75%RH.

6. CONCLUSION

The TCI levels for all of the oxaliplatin in sugar solutions investigated are between 2-3 times higher than the TCI level obtained for oxaliplatin in water after 3 months at 40°C/75%RH.

Addition of sugars (reducing and non-reducing) to the oxaliplatin in water formulation does not enhance the stability of the current aqueous oxaliplatin solution formulation.

**Appendix 1 : Experimental Protocol For Stability Of Oxaliplatin In The Presence Of
Dissolved Sugars**

Experimental Protocol For Stability of Oxaliplatin In The Presence of Dissolved Sugars

1. OBJECTIVE

To determine if the addition of reducing sugars to aqueous solutions of oxaliplatin enhance the chemical stability of the solution compared to the current aqueous oxaliplatin solution formulation (drug in water).

If a positive effect on stability is achieved, then data from this study will be used to support a patent application.

2. BACKGROUND

Oxaliplatin is known to undergo oxidative degradation in aqueous solution.

The addition of reducing sugars may act as an alternative route of oxidation in the system and therefore prevent or minimize oxidative degradation of oxaliplatin solution.

Stability studies of the reconstituted lyophilised product, which contains lactose, have not detected the impurities associated with the oxidative degradation of oxaliplatin (albeit after only 48 hours storage).

It has been postulated that the lactose molecule may form a loose structure ("cage") around oxaliplatin preventing degradation. The addition of non-reducing sugars may act in the same way.

The sugars selected are based on:

- the pharmacopoeial status
- use in injectable products
- association with lyophilised product
- ability to act as reducing sugar (sucrose is a non-reducing sugar and is included as a control to observe the effect of sugars independent of their ability to reduce).

The sugar concentration selected for this study is 5% w/v, which is an excess to allow interpretation of data from this screening exercise. A positive result will initiate further testing to optimise sugar concentration. The 5% w/v concentration is a typical value for maintaining isotonicity of the product with plasma, and therefore is considered a maximum to avoid producing a hypertonic solution.

The sugars listed in Table (2.) 1 will be investigated in this study.

Table (2.) 1 - Sugars To Be Studied

| Sugar | Rationale For Inclusion |
|---------|--|
| Lactose | Pharmacopoeial (EP, USP,NF), present in lyophilised product, reducing sugar, used in injectables disaccharide |
| Glucose | Pharmacopoeial (BP, JP, Ph Eur, USP), Used to reconstitute/dilute lyophilised product, reducing sugar, monosaccharide |
| Maltose | Pharmacopoeial (JP), reducing sugar, used in injectables, disaccharide |
| Sucrose | Pharmacopoeial (BP, JP, Ph Eur, USP), non-reducing sugar, used in injectables, disaccharides |

3. STUDY DESIGN

The oxaliplatin concentration used in this study will be 5 mg/mL (oxaliplatin concentration in the current aqueous solution and lyophilised product).

An aqueous 5 mg/mL oxaliplatin in water solution will also be prepared as a control for this study.

Control sugar solutions (sugar in water) will be prepared for each of the sugars investigated (see table (2.) 1). This is to provide blank solutions for the HPLC analysis (assay and TCI).

3.1 Formulations And Presentations To Be Studied

- Formulation 1 – oxaliplatin 5 mg/mL in water
 - Formulation 2 – oxaliplatin 5 mg/mL in 5% w/v lactose
 - Formulation 3 – oxaliplatin 5 mg/mL in 5% w/v glucose
 - Formulation 4 – oxaliplatin 5 mg/mL in 5% w/v maltose
 - Formulation 5 – oxaliplatin 5 mg/mL in 5% w/v sucrose
 - Formulation 6 – 5% w/v lactose in water
 - Formulation 7 – 5% w/v glucose in water
 - Formulation 8 – 5% w/v maltose in water
 - Formulation 9 – 5% w/v sucrose in water
-
- Presentation – Fill 4 mL of the oxaliplatin 5 mg/mL solution into a 16 mL type I clear glass vial, with 19 mm Flurotec bromobutyl stopper and sealed with 20 mm aluminium flip-off cap.
-
- Pack Orientation – Vials should be stored upright.

3.2 Storage Conditions And Timepoints To Be Tested

Samples will be stored at the following conditions: -

- 5°C – to provide refrigerated storage data if required,
- 25°C/60%RH – to provide real time data,
- 40°C/75%RH – to provide accelerated data.

Testing will be carried out initially and after 30 days (at 25°C/60%RH and 40°C/75%RH), at which time the data will be reviewed to determine if a positive effect on the stability of the solutions has been achieved. If a positive result is achieved, the data will be submitted to the patents department.

Testing of all other samples will be placed on hold and only activated if required to strengthen the patent application.

Sufficient samples will be placed at 25°C/60%RH and 40°C/75%RH for 4 timepoints, and at 5°C for 2 timepoints.

3.3 Solution Preparation

3.3.1 Materials

- a) Oxaliplatin – Prodstar Item no: D008387, Lot no: 99-02064
- b) Lactose monohydrate 200 mesh Ph Eur, NF – Prodstar Item no: A000722, Lot no: AR032172
- c) D-(+)-Glucose anhydrous – SigmaUltra (99.5%), Lot: 80K1014
- d) Maltose monohydrate – SigmaUltra (minimum 99%), Lot: 80K10101
- e) Sucrose – SigmaUltra (>99.5%), Lot: 51K0026
- f) Water for Injections Ph Eur, USP – Prodstar Item no: A002627, Lot no: AR034049
- g) PVDF 0.22µm filter media, Millipore, Durapore 47mm GVWP04700
- h) Disposable sterile plastic syringes
- i) Disposable sterile needles
- j) Disposable sterile 1.2 µm filters (Minisart)
- k) 16mL Schott Amphabel, tubular, type I, clear glass vial – Prodstar Item no: A001731, Lot no: AR017373
- l) West Flurotec, 19mm bromobutyl stopper with B2-40 coating – Prodstar Item no: A009258, lot no: AR020196
- m) Aluminium seals - 20mm flip-off cap, translucent in colour – Prodstar Item no: A005246, Lot no: AR016305

3.3.2 Equipment

- a) Mettler AT261 balance - P/N 41451
- b) Mettler AT460 balance - P/N 27329
- c) Jenway 3410 Electrochemistry Analyser - P/N 26474
- d) IKAMAG Magnetic/hotplate stirrer - P/N 41207
- e) Isolator - cabinet 19
- f) Class II cabinet - cabinet 20
- g) Schubert Crimper - P/N 26084

3.3.3 Solution Composition

The composition of the oxaliplatin solution formulations and the sugar control solutions are described in table (3.3.3) 1.

Table (3.3.3) 1 - Composition Of Solutions To Be Investigated

| Formulation Number | Material | | | | | |
|--------------------|-------------|----------|----------|----------|----------|---------|
| | Oxaliplatin | Lactose | Glucose | Maltose | Sucrose | W.F.I. |
| 1 | 5 mg/mL | - | - | - | - | to 1 mL |
| 2 | 5 mg/mL | 50 mg/mL | - | - | - | to 1 mL |
| 3 | 5 mg/mL | - | 50 mg/mL | - | - | to 1 mL |
| 4 | 5 mg/mL | - | - | 50 mg/mL | - | to 1 mL |
| 5 | 5 mg/mL | - | - | - | 50 mg/mL | to 1 mL |
| 6 | - | 50 mg/mL | - | - | - | to 1 mL |
| 7 | - | - | 50 mg/mL | - | - | to 1 mL |
| 8 | - | - | - | 50 mg/mL | - | to 1 mL |
| 9 | - | - | - | - | 50 mg/mL | to 1 mL |

The quantities of each material required to prepare a 250 mL batch of each oxaliplatin solution formulation is listed in table (3.3.3) 2.

Table (3.3.3) 2 – Quantities Of Materials Required To Prepare 250 mL Of Each Oxaliplatin Formulation

| Formulation Number | Material | | | | | |
|--------------------|-------------|---------|---------|---------|---------|-----------|
| | Oxaliplatin | Lactose | Glucose | Maltose | Sucrose | W.F.I. |
| 1 | 1.25 g | - | - | - | - | to 250 mL |
| 2 | 1.25 g | 12.5 g | - | - | - | to 250 mL |
| 3 | 1.25 g | - | 12.5 g | - | - | to 250 mL |
| 4 | 1.25 g | - | - | 12.5 g | - | to 250 mL |
| 5 | 1.25 g | - | - | - | 12.5 g | to 250 mL |

The quantities of each material required to prepare a 100 mL batch of each sugar (control) formulation is listed in table (3.3.3) 3.

Table (3.3.3) 3 - Quantities Of Materials Required To Prepare 100 mL Of Each Sugar Formulation

| Formulation Number | Material | | | | |
|--------------------|----------|---------|---------|---------|-----------|
| | Lactose | Glucose | Maltose | Sucrose | W.F.I. |
| 6 | 5.00 g | - | - | - | to 100 mL |
| 7 | - | 5.00 g | - | - | to 100 mL |
| 8 | - | - | 5.00 g | - | to 100 mL |
| 9 | - | - | - | 5.00 g | to 100 mL |

3.4 Preparation Method For The Oxaliplatin Solutions

3.4.1 Preparation Method For Formulation 1 – Oxaliplatin 5 mg/mL In Water

- Dispense > 250 mL of Water For Injections (W.F.I.), heat up to 40°C using a magnetic hotplate/stirrer.
- Transfer 170 mL of the W.F.I. into a 250 mL Schott bottle. Set aside the remainder (~80 mL) to make up final volume.
- Weigh the Oxaliplatin drug substance into a small glass beaker and transfer into the Schott bottle (rinsing with ~ 40 mL of hot (40°C) W.F.I.).
- Stir on the magnetic stirrer (keeping the temperature at 40°C) until all of the solids have dissolved.
- Allow the solution to cool to room temperature, then transfer the solution to a 250 mL volumetric flask and make up to 250 mL with cool (~20°C) W.F.I.
- Measure the pH of the solution (for information only).
- Filter the solution into a Buchner flask, through a Millipore type GV, 47 mm diameter, 0.22 µm filter, using the vacuum line.
- Fill 4 mL of solution into 16 mL glass vials, using a syringe fitted with a sterile 1.2 µm disposable filter (Minisart). Stopper the vials with 19 mm Flurotec stoppers and then seal with 20 mm aluminium seals.
- Label the vials with name of formulation, batch number, hazard rating and date prepared.

3.4.2 Preparation Method For Formulations 2 to 5 –Oxaliplatin 5 mg/mL In Various Sugars

- Dispense > 250 mL of Water For Injections (W.F.I.), heat up to 40°C using a magnetic hotplate/stirrer.
- Transfer 170 mL of the W.F.I. into a 250 mL Schott bottle. Set aside the remainder (~80 mL) to make up final volume.

- c) Weigh the appropriate sugar (see table (3.3.3) 2) into a small beaker and transfer into the Schott bottle (rinsing with ~ 30 mL of hot (40°C) W.F.I.).
- d) Stir on the magnetic stirrer (keeping the temperature at 40°C) until all of the solids have dissolved.
- e) Weigh the Oxaliplatin drug substance into a small glass beaker and transfer into the Schott bottle (rinsing with ~ 40 mL of hot (40°C) W.F.I.).
- f) Stir on the magnetic stirrer (keeping the temperature at 40°C) until all of the solids have dissolved.
- g) Allow the solution to cool to room temperature, then transfer the solution to a 250 mL volumetric flask and make up to 250 mL with cool (~20°C) W.F.I.
- h) Measure the pH of the solution (for information only).
- i) Filter the solution into a Buchner flask, through a Millipore type GV, 47 mm diameter, 0.22 µm filter, using the vacuum line.
- j) Fill 4 mL of solution into 16 mL glass vials, using a syringe fitted with a sterile 1.2 µm disposable filter (Minisart). Stopper the vials with 19 mm Flurotec stoppers and then seal with 20 mm aluminium seals.
- k) Label the vials with name of formulation, batch number, hazard rating and date prepared.

3.5 Preparation Method For The Sugar (Control) Solutions

3.5.1 Preparation Method For Formulations 6 to 9

- a) Weigh the appropriate sugar (see table (3.3.3) 3) into a 150 mL glass beaker and add ~80 mL of W.F.I.
- b) Stir on a magnetic stirrer until all of the solids dissolve.
- c) Transfer the solution to a 100 mL volumetric flask and make up to 100 mL with W.F.I.
- d) Measure the pH of the solution (for information only).
- e) Filter the solution into a Buchner flask, through a Millipore type GV, 47 mm diameter, 0.22 µm filter, using the vacuum line.
- f) Fill 4 mL of solution into 16 mL glass vials, using a syringe fitted with a sterile 1.2 µm disposable filter (Minisart). Stopper the vials with 19 mm Flurotec stoppers and then seal with 20 mm aluminium seals.
- g) Label the vials with name of formulation, batch number, hazard rating and date prepared.

4. TEST CONDITIONS AND ANALYSIS OF SAMPLES

The vials will be removed from the relevant storage condition by PSD.

- PSD will visually inspect the vials of solution before giving them to ASD for analysis.
- ASD will analyse the vials of solution for assay and total chromatographic impurities (TCI).

4.1 Number Of Vials Of Each Formulation Required At Each Timepoint

4.1.1 Number Of Oxaliplatin Solution Vials (Formulations 1 to 5) Required At Each Timepoint

Table (4.1.1) 1 - Number Of Oxaliplatin Vials Required

| | Number Of Vials | | | | Total |
|--------------|-----------------|---------|---------|---------|-----------------|
| | Initial | 30 days | 90 days | On hold | |
| 5°C | - | - | - | 10 | 10 |
| 25°C/60%RH | 5 | 5 | - | 15 | 25 |
| 40°C/75%RH | - | 5 | - | 15 | 20 |
| TOTAL | | | | | 55 Vials |

Note: 5 vials (4 mL fill) are required at each timepoint to conduct assay and TCI analysis.

4.1.3 Number Of Sugar Solution Vials (Formulations 6 to 9) Required At Each Timepoint

Table (4.1.2) 1 - Number Of Sugar Control Vials Required

| | Number Of Vials | | | | Total |
|--------------|-----------------|---------|---------|---------|-----------------|
| | Initial | 30 days | 90 days | On hold | |
| 5°C | - | - | - | 4 | 4 |
| 25°C/60%RH | 2 | 2 | - | 6 | 10 |
| 40°C/75%RH | - | 2 | - | 6 | 8 |
| TOTAL | | | | | 22 Vials |

Note: 2 vials (4 mL fill) are required at each timepoint to provide a control (blank) for the assay and TCI analysis of the oxaliplatin formulations.

4.2 Batch Size Required For Each Formulation

4.2.1 Batch Size Required For Each Oxaliplatin Solution Formulation (1 to 5)

A total of 220 mL (55 x 4 mL fill) of each oxaliplatin solution formulation is required to conduct the study. Hence, a batch size of 250 mL should be prepared for each formulation and any spare vials placed at 25°C/60%RH. This will use a total of 6.25 g of oxaliplatin drug substance (1.25 g per formulation x 5).

4.2.2 Batch Size Required For Each Sugar (Control) Solution Formulation (6 to 9)

A total of 88 mL (22 x 4 mL fill) of each sugar solution formulation is required to conduct the study. Hence, a batch size of 100 mL should be prepared for each formulation and any spare vials placed at 25°C/60%RH.

5. ACCEPTANCE CRITERIA AND RATIONAL

Compliance with the acceptance criteria indicates that the addition of sugars to oxaliplatin solution enhances the chemical stability of the solution compared to the current aqueous oxaliplatin solution formulation (drug in water), and as such represents an opportunity to patent a formulation improvement.

5.1 Acceptance Criteria

The analytical results should remain within the following specification, which is related to the aqueous oxaliplatin solution product.

- 1) Visual Appearance – clear, colourless solution with no particles
- 2) Assay – should remain within $\pm 5\%$ of initial assay
- 3) Total Chromatographic Impurities (TCI) – should be significantly better than the oxaliplatin in water control (Formulation 1)

If any of the oxaliplatin/sugar solution formulations fail to meet the acceptance criteria listed above then they should be discarded from the study.

If any of the oxaliplatin/sugar solution formulations exhibit improved chemical stability (in terms of lower impurity levels) compared to the oxaliplatin in water solution

formulation (Formulation 1), then data should be submitted for consideration as a patent application.

Prepared by: - A. Miller *Allen Miller* 11th February 2002
PSD Approval: - E. Baker *E. Baker* 11th February 2002
ASD Approval: - M. Gray *M. Gray* 11/2/02