



(43) International Publication Date
8 December 2016 (08.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/191820 A1

(51) International Patent Classification:

A61K 31/573 (2006.01) A61P 41/00 (2006.01)
A61K 47/36 (2006.01) A61K 9/00 (2006.01)

(21) International Application Number:

PCT/AU2016/050445

(22) International Filing Date:

2 June 2016 (02.06.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2015902089	2 June 2015 (02.06.2015)	AU
2015902669	7 July 2015 (07.07.2015)	AU
2015903087	3 August 2015 (03.08.2015)	AU

(71) Applicant: **NEWSOUTH INNOVATIONS PTY LIMITED** [AU/AU]; Rupert Myers Building, Gate 14, Barker Street, UNSW, Sydney, New South Wales 2052 (AU).

(72) Inventors: **EVISTON, Timothy J.**; 1/54 Coogee Bay Road, Randwick, New South Wales 2031 (AU). **KRISHNAN, Arun**; 335 Avoca Street, Randwick, New South Wales 2031 (AU).

(74) Agent: **GRIFFITH HACK**; Level 29 Northpoint, 100 Miller Street, North Sydney, New South Wales 2060 (AU).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: FORMULATION AND PROCESS FOR LIMITING NERVE TRAUMA

(57) Abstract: Disclosed in some forms is a process of limiting the impact of surgery on a nerve, the process comprising applying a therapeutic substance to the nerve during surgery. In some aspects, disclosed is a formulation for reducing nerve trauma comprising an active pharmacological ingredient adapted to intervene in the activation of pathways of cellular degradation within the nerve and a carrier adapted to reduce dissemination of the active pharmacological ingredient beyond the site at which its effect is intended.



WO 2016/191820 A1

- 1 -

FORMULATION AND PROCESS FOR LIMITING NERVE TRAUMA

BACKGROUND

The present invention relates to limiting trauma to a
5 nerve, and to a formulation, delivery system and process
for limiting trauma to a nerve. The formulation and
process particularly limit the impact of surgery or other
event or activity on a nerve, however the formulation and
process are not limited to those applications. The
10 delivery system is particularly suited to delivering a
therapeutic substance during surgery but is not limited to
that application

SUMMARY

15

Disclosed in some forms is a process of limiting the
impact of surgery on a nerve, the process comprising
applying a therapeutic substance to the nerve during
surgery.

20

In some forms the therapeutic substance is selected from
substances that can intervene in the activation of
pathways of cellular degradation within the nerve.

25 In some forms the therapeutic substance comprises an
active pharmacological ingredient and a carrier.

The process has the benefit of limiting nerve trauma for
patients during surgery or dental surgery by providing a
30 predictable localisation and consistent rate-limited
delivery of an active pharmaceutical ingredient that
reduces the trauma on nerves through surgery. The delivery

- 2 -

of the active pharmaceutical ingredient directly to the nerve during surgery improves nerve function and repair post surgery.

- 5 In some aspects, disclosed is a formulation for reducing nerve trauma comprising an active pharmacological ingredient adapted to intervene in the activation of pathways of cellular degradation within the nerve and a carrier adapted to reduce dissemination of the active
10 pharmacological ingredient beyond the site at which its effect is intended.

The formulation includes an active pharmaceutical ingredient and a carrier that provides benefits such as
15 slow release and localisation of the active pharmaceutical. The active pharmaceutical ingredient therefore is more likely to remain on the intended site of effect.

- 20 In other aspects, disclosed is use of a formulation as described during surgery.

In some forms the use comprises applying the formulation to a nerve that has been exposed during surgery.

- 25 Disclosed in some forms is a method of delivering a therapeutic substance during surgery, the method comprising loading a solid phase or gel phase biodegradable scaffold with a therapeutic substance; and
30 positioning the scaffold during surgery such that the therapeutic substance is delivered to a desired location.

- 3 -

During surgery, internal delivery sites for therapeutic substances are exposed allowing for positioning of a scaffold to allow positioning of the material such that it remains in one place, and delivery of the substance over a
5 period of time at a sustained rate.

In some forms the therapeutic substance is selected from substances that can intervene in the activation of pathways of cellular degradation within the nerve and the
10 desired location is proximal to a nerve.

In some forms the method allows for delivery of a therapeutic substance and a haemostatic agent in combination.
15

In other aspects, disclosed is a system for delivering a therapeutic substance during surgery, the system comprising a solid phase biodegradable scaffold with a therapeutic substance loaded thereon.
20

The method and system may provide for improved levels of pain management, improved delivery of the therapeutic substance, improved recovery, improved muscle function, improved autonomy, or improved sensation. In some forms
25 chronic pain or inflammation can be reduced or avoided. In some forms delivery of the drug beyond a selected site is minimised.

In some forms the method of delivery allows
30 differentiation of delivery of different therapeutic substances.

- 4 -

In some forms, disclosed is a formulation comprising an active pharmacological ingredient having a neuroprotective effect and a carrier adapted to reduce dissemination of the active pharmacological ingredient beyond the site at
5 which its effect is intended.

In some forms, disclosed is a process of protecting a nerve during surgery, the process comprising identifying a nerve using a nerve monitor and applying a therapeutic
10 substance to the nerve. In some form the process further comprises the step of monitoring the nerve function by monitoring EMG activity from muscles innervated by the affected nerve.

15 The process, formulation and delivery system may provide for improved levels of pain, improved recovery, improved muscle function, improved autonomy, or improved sensation. In some forms chronic pain or inflammation can be reduced
20 or avoided. They may provide for improved effectiveness of treatment.

BRIEF DESCRIPTION OF THE FIGURES

25 The disclosure will be described in view of the Figures,

Fig 1 is a graphical representation of molecular weight v time for hyaluronic acid with dexamethasone as in some embodiments of the disclosure;

30 Fig 2 is a graphical representation of molecular weight v time for hyaluronic acid with dexamethasone as in some embodiments of the disclosure;

- 5 -

Fig 3 graphical representation of drug stability v time for dexamethasone in the presence of excipients as in some embodiments of the disclosure;

Fig 4 is a graphical representation of drug stability v time for dexamethasone with hyaluronic acid as in some embodiments of the disclosure.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE DISCLOSURE

10

Disclosed in some forms is a process of limiting the impact of surgery on a nerve, the process comprising applying a therapeutic substance to the nerve during surgery.

15

In some forms the therapeutic substance is selected from substances that can intervene in the activation of pathways of cellular degradation within the nerve. In some forms the formulation interrupts or downregulates intra-axonal pathways of cell death or degradation during the course of a surgical procedure. In some forms the therapeutic substance has a neuroprotective effect.

20

In some forms the therapeutic substance comprises an active pharmacological ingredient and a carrier.

25

In some forms the carrier is a depot matrix. In some forms the carrier is adapted to slow the release of the active pharmacological ingredient.

30

In some forms the carrier has a consistency and rheology adapted to reduce dissemination of the active

- 6 -

pharmacological ingredient beyond the site at which its effect is intended.

In some forms the carrier is adapted to localise the
5 active pharmacological ingredient to the site at which its effect is intended.

In some forms the active pharmacological ingredient is a corticosteroid. In some forms the pharmacological
10 ingredient is dexamethasone.

In some forms the active pharmacological ingredient is hydrocortisone, methylprednisone, triamcinolone, Betamethasone or any other corticosteroid.

15 In some forms the active pharmacological ingredient is any of a number of medications which have a neuroprotective effect or act to decrease nerve dysfunction. This may include any one or more of 4-Aminopyridine (or derivatives
20 eg. Fampridine), Riluzole, NAD altering molecules such as nicotinamide mononucleotide, CD38 and cyclic ADP ribose hydrolase inhibitors, nicotinamide riboside, AICAR, resveratrol, thiazolidinediones (eg. rosiglitazone, pioglitazone etc), metformin, local anaesthetics (eg.
25 bupivacaine), cyclosporin, tacrolimus, COX inhibitors (eg. ketorolac, diclofenac), calcium channel blockers (eg. nifedipine), pipaverine, dexpramiprexole.

In some forms the active pharmacological acts by improving mitochondrial function or inhibiting calcium or cell death
30 pathways.

Surgical nerve injury peripheral to the surgery is a

- 7 -

danger of surgery. Nerve dysfunction can result from trauma to the nerves despite the nerves appearing to be intact. This makes nerve dysfunction difficult to predict during surgery. Traumatic mechanisms such as stretch,
5 thermal injury, electrical injury, compression and ischaemia can accumulate to cause activation of pathways of cellular degradation within a nerve's axon. This can cause nerve break down and loss of function.

10 The process of controlled application of a formulation directly to a nerve that can intervene in pathways of cellular degradation has the impact of reducing the potential of trauma to the nerve or reducing the effects of that trauma. This trauma can occur even in
15 circumstances where that trauma is not visible. Thus application of dexamethasone or an alternative active pharmaceutical ingredient to a nerve during surgery can limit or prevent peripheral nerve injury occurring during surgery.

20 In some forms the step of applying a therapeutic substance to the nerve is performed upon exposure of the nerve during surgery.

25 In some forms, the step of applying a therapeutic substance to the nerve is performed using a delivery device comprising a reservoir and an outlet, the therapeutic substance being delivered through the outlet.

30 In some forms actuation of the delivery device effects delivery of the formulation during the time at which the actuator is actuated.

- 8 -

Further, disclosed is a formulation for reducing nerve trauma comprising an active pharmacological ingredient adapted to intervene in the activation of pathways of cellular degradation within the nerve and a carrier adapted to slow release to prolong the pharmacokinetics of the active pharmaceutical, and to reduce dissemination of the active pharmaceutical ingredient beyond the site at which its effect is intended.

10

In some forms the active pharmacological ingredient is effective to limit nerve dysfunction or have a neuroprotective impact.

15 The active pharmaceutical ingredient may also include a prodrug, biologic, immunoglobulin, viral vector, gene therapy, immunotherapy, DNA plasmid, RNA inhibitor or protein or peptide.

20 The formulation allows the application of an active pharmaceutical ingredient to a nerve while limiting the application of that ingredient to surrounding cells. This may provide greater concentration of the active pharmaceutical to the relevant cells and limits waste. The formulation can also act to slow release of the active pharmaceutical ingredient.

The formulation, in some embodiments of the disclosure, comprises a corticosteroid such as dexamethasone in the form of dexamethasone phosphate or dexamethasone sodium phosphate in hyaluronic acid. In some forms the formulation comprises dexamethasone sodium phosphate, in a

30

- 9 -

hydrogel of hyaluronic acid. In some forms the formulation further includes any one of more of the excipients creatinine, sodium citrate, sodium sulphate, methyl paraben, propylparaben. In some forms the hyaluronic acid
5 may be cross-linked using a process such as divinyl sulfone or similar cross-linking technology. In some forms the hyaluronic acid may be esterified.

In some forms, the formulation includes a marker such as a
10 visual or fluorescent marker. Example markers could include biocompatible excipients or food dyes such as brilliant blue (FD&C Blue #1), indigo carmine or similar, antioxidants such as ascorbic acid, fluorescent markers such as Fluorescein, indocyanine green (ICG),
15 protoporphyrin IX or other surgical dyes such as patent blue V, trypan blue, isosulfan blue or methylene blue. The use of a marker gives a surgeon a visual cue to indicate the presence of the formulation on a nerve. This may aid the user in applying the formulation under-vision and to
20 prevent repeated dosing over the same site. In some forms this enables the future identification of the labelled nerve and/or allows intra-axonal transport to delineate target organs or cell bodies for a particular nerve.

25 Also disclosed is use of a formulation as described during surgery. In some forms the use comprises applying the formulation to a nerve that has been exposed during surgery.

30 Disclosed in some forms is a composition comprising hyaluronic acid and dexamethasone. The composition in some

- 10 -

forms is for use in the treatment and protection of nerves during surgery.

In some forms the hyaluronic acid is in the concentration
5 of between 1% and 3% w/w. In some forms the concentration of hyaluronic acid is between approximately 10mg/mL and 50mg/mL, in some forms the concentration is 30mg/mL.

In some forms the hyaluronic acid is in the form of sodium
10 hyaluronate with a Molecular weight of 0.9 MDa(0.8-1.0) or a molecular weight of 2.1MDa (2.0-2.3 MDa) But may be within the range 7 to 2300kDa.

In some forms the formulation comprises hyaluronic acid
15 with a substantially consistent molecular weight of approximately 0.9 MDa or a substantially consistent molecular weight of approximately between 0.8 and 1.0 MDa. In this form the formulation may have a concentration of approximately 5% w/w. In this form the formulation may
20 include dexamethasone at a concentration of approximately 1mg/mL.

In some forms the formulation comprises hyaluronic acid with a substantially consistent molecular weight of
25 approximately 2.1 MDa or a substantially consistent molecular weight of approximately between 2.0 and 3.0 MDa. In this form the formulation may have a concentration of approximately 3% w/w. In this form the formulation may also include dexamethasone at a concentration of
30 approximately 1mg/mL.

- 11 -

In some forms the carrier may be an oligosaccharide of sodium hyaluronate. In some forms the carrier may be a sodium hyaluronate nanofibre or microfiber.

5 In some forms, the carrier has a consistent molecular weight and a consistent concentration. A consistent molecular weight in combination with a consistent concentration results in a reproducible viscosity and rheology.

10

In some forms the dexamethasone is in the form of dexamethasone phosphate. In some forms the dexamethasone phosphate is in the concentration of between 0.1mg/mL and 10.0mg/mL. In some forms the dexamethasone phosphate is in
15 the concentration of approximately 1 mg/mL. In some forms the dexamethasone phosphate is in a concentration of 4mg/mL.

In some forms the hyaluronic acid has a weight percentage
20 between 0.5% and 5% w/w. In some forms the weight percentage of hyaluronic acid in the formulation is between 1% and 3%. In some forms the weight percentage of hyaluronic acid in the formulation is approximately 2%.

25 In some forms the dexamethasone is in the form of dexamethasone sodium phosphate. In some forms the dexamethasone sodium phosphate is in the concentration of between 0.5mg/mL and 4.0mg/mL. In some forms the dexamethasone sodium phosphate is in the concentration of
30 approximately 1 mg/mL.

- 12 -

In some forms the composition further comprises one or more of creatinine, sodium citrate, sodium disulfite, methyl paraben, propyl paraben.

- 5 Further disclosed is use of a composition comprising hyaluronic acid and dexamethasone in the manufacture of a medicament for treatment and protection of nerves during surgery.
- 10 Disclosed is a method of treatment of an exposed nerve comprising delivering a composition comprising:
a matrix having one or more of a slow release effect and a viscosity that encourages maintenance of the location of the composition in the delivery location and
15 a pharmacological active having one or more of a neuroprotective effect and a reduction of nerve dysfunction;
to an exposed nerve.
- 20 In some forms the matrix comprises a partially cross-linked hyaluronan hydrogel. In some forms the matrix has a pH = 6.9-7.5. In some forms the hyaluronic acid has a concentration of approximately 1.5-2.0 % w/w.
- 25 In some forms the rheology of the matrix limits the flow of the active away from a site of delivery. In some forms this allows for extended therapeutic effects. In some forms the elastic modulus of the matrix is between 100-200 Pa.
- 30 In some forms the carrier or matrix is adapted to slow release, to prolong the pharmacokinetics of the active

- 13 -

pharmaceutical, and to reduce dissemination of the active pharmaceutical ingredient beyond the site at which its effect is intended. This may provide greater concentration of the active pharmaceutical to the relevant cells and
5 limits waste.

In some forms the method comprises using a delivery device to deliver the composition.
10

In some forms the method is used in conjunction with a nerve monitor to enhance the process of locating a particular nerve and allow accurate deposit of the
15 therapeutic formulation to the nerve. This provides a complete nerve solution by utilising both a diagnostic tool and a therapeutic formulation to treat and protect a nerve. Nerve monitors enable surgeons to identify, confirm, and monitor motor nerve function to help reduce
20 the risk of nerve damage during various procedures.

Disclosed in some forms is a process for delivering a therapeutic substance during surgery. The method comprises loading a solid phase biodegradable scaffold with a
25 therapeutic substance; positioning the scaffold during surgery such that the therapeutic substance is delivered to a desired location.

In some forms the therapeutic substance is selected from
30 substances that can intervene in the activation of pathways of cellular degradation within the nerve.

- 14 -

In some forms the desired location is proximal or adjacent to a nerve. In some forms the therapeutic substance may be brought in contact with the nerve and/or allowed to coat the nerve.

5

In some forms the step of positioning the scaffold is performed upon exposure of the nerve during surgery.

In some forms the therapeutic substance is dexamethasone.

10

In some forms the therapeutic substance comprises a formulation comprising a biodegradable carrier and a therapeutic ingredient advantageous during tonsillectomy or sinus surgery.

15

In some forms the therapeutic ingredient comprises a local anaesthetic.

In some forms the therapeutic ingredient comprises an anti-inflammatory agent.

20

In some forms the therapeutic ingredient comprises an antibiotic.

25 In some forms the therapeutic ingredient comprises a haemostatic agent.

- 15 -

In some forms the therapeutic substance comprises a formulation comprising a biodegradable carrier and a therapeutic ingredient advantageous in treatment of burns or skin loss.

5

In some forms the therapeutic substance comprises a formulation comprising a biodegradable carrier and a chemotherapy agent.

10 Positioning of a chemotherapy agent during surgery allows for work around vital structures. For example when a cancer is located around a significant nerve the surgeon will wish to avoid damaging the nerve. The method allows for a long acting chemotherapy agent to be left on a
15 tumour or evidence of residual disease for long term treatment.

Further, disclosed is a system comprising a solid phase biodegradeable scaffold with a therapeutic substance
20 loaded thereon.

In some forms the scaffold further is further loaded with a haemostatic agent.

25 In some forms the therapeutic substance is selected from substances that can intervene in the activation of pathways of cellular degradation within the nerve.

In some forms the therapeutic substance is dexamethasone.

30

In some forms the carrier on which the therapeutic ingredient is loaded onto the scaffold is adapted to allow

- 16 -

for ease of application of the therapeutic substance and associated pharmacological ingredient to a designated site during surgery and for concentration and efficiency. The carrier is, in some forms, adapted to reduce dissemination
5 of the active pharmacological ingredient beyond the site at which its effect is intended. In some forms the carrier is adapted to localise the active pharmacological ingredient to the site at which its effect is intended.

10 The process allows controlled application of a therapeutic substance directly to a location such as a nerve, a burn site, a surgical site or a cancer. The application can limit or prevent peripheral damage, trauma or injury occurring during surgery and limit flow of the therapeutic
15 substance beyond the intended site.

In some forms the step of applying the scaffold loaded with the therapeutic substance to the nerve is performed upon exposure of the nerve during surgery.

20

In some forms, the step of applying a therapeutic substance to the nerve is performed using a delivery device comprising a reservoir and an outlet, the therapeutic substance being delivered through the outlet.

25

In some forms actuation of the delivery device effects delivery of the formulation during the time at which the actuator is actuated.

30 The carrier in some forms is adapted to slow release, to prolong the pharmacokinetics of the active pharmaceutical, and to reduce dissemination of the active pharmaceutical

- 17 -

ingredient beyond the site at which its effect is intended. This may provide greater concentration of the active pharmaceutical to the relevant cells and limits waste.

5

The carrier, in some forms, comprises natural polymers for example copolymers such as poly(lactic-co-glycolic acid), alginate, proteins, collagens, gelatin, fibrins, hyaluronan, polysaccharides, and albumin, or other
10 synthetic polymers.

In some forms, the formulation includes a marker such as a visual or fluorescent marker. The use of a marker gives a surgeon a visual cue to indicate the presence of the
15 formulation on a site. In some forms this enables the future identification of the labelled site and/or allows delineation of target sites.

The process and system are specifically described in
20 relation to delivery of a formulation that can intervene in pathways of cellular degradation of a nerve or be used in treatment during tonsillectomy or sinus surgery, in treatment of burns or skin loss or in treatment of cancer through a chemotherapy agent during surgery. However it
25 will be clear that the process of delivery can be utilised beyond the described circumstances.

Biocompatible materials used for fabrication of scaffolds for the purposes of delivery of a therapeutic substance
30 may comprise natural polymers for example copolymers such as poly(lactic-co-glycolic acid), alginate, proteins, collagens, gelatin, fibrins, and albumin, or other

- 18 -

synthetic polymers. In some forms the polymer comprises re-oxidised cellulose. In other forms bioceramics such as hydroxyapatites and tricalcium phosphates are used.

5 The structures are porous to allow delivery of drugs and genetic materials at a controlled rate over a period of time.

In some forms antibiotics or anti-inflammatory agents may
10 be loaded onto the scaffold to prevent infection or inflammation after surgery.

In some forms the therapeutic substance is loaded through a biodegradable carrier such as hyalauronic acid for
15 gradual sustained release.

Disclosed in some forms is a formulation comprising an active pharmacological ingredient having a neuroprotective effect and a carrier adapted to reduce dissemination of
20 the active pharmacological ingredient beyond the site at which its effect is intended.

In some forms the active pharmacological ingredient is a corticosteroid.
25

In some forms the carrier is a depot matrix.

EXAMPLES

30

The following formulations are exemplary only and other formulations with alternative carriers, alternative active

- 19 -

pharmaceuticals, alternative excipients and alternative concentrations will fall inside the scope of the claims and the scope of the disclosure.

5 **Example 1:**

In the first example the formulation comprises hyaluronic acid in the form of Hyasis® 850 (10.0 mg/mL), dexamethasone sodium phosphate (4.0 mg/mL), creatinine, sodium citrate, sodium disulfite, methyl paraben, propyl
10 paraben (pH 6.8)

The formulation was stored at 5, 25, and 37 °C for 210 days and the Hyaluronic Acid molecular weight was measured by SECMAIS

15

Results

No significant polymer degradation was observed up to 210 days at 5 and 25°C

20 Significant degradation was observed after 18 days at 37°C most likely due to one or several excipients and/or their degradation products and the degradation products of dexamethasone (according to control experiments)

25 Figure 1 shows the results in graphical form.

Example 2:

Formulation: hyaluronic acid (10.0 mg/mL), dexamethasone
30 sodium phosphate (4.0 mg/mL) (pH 6.8)

The formulation was stored at 5, 25, and 37 °C for 210

- 20 -

days and the Hyaluronic Acid molecular weight was measured by SECMAIS

Results

- 5 No hyaluronic acid degradation was observed up to 210 days at 5 and 25°C. Dexamethasone and/or its degradation products most likely resulted in significant hyaluronic acid degradation after 30 days at 37°C
- 10 Figure 2 shows the results in graphical form.

Example 3:

Formulation

- 15 Dexamethasone sodium phosphate (4.0 mg/mL), creatinine, sodium citrate, sodium disulfite, methyl paraben, propyl paraben (pH 6.8)

The formulation was stored at 5, 25, and 37 °C for
20 91 days and drug stability was assessed by HPLC

Results:

- 25 No drug degradation was observed up to 91 days at 5 and 25°C. Heat and/or one or several excipients and/or their degradation products most likely resulted in significant API degradation after 28 days at 37°C.
- 30 Figure 3 shows the results in graphical form.

Example 4:

- 21 -

Formulation: hyaluronic acid (10.0 mg/mL), dexamethasone sodium phosphate (4.0 mg/mL) (pH 6.8)

5 The formulation was stored at 5, 25, and 37 °C for 91 days and drug stability was assessed by HPLC

Results:

No drug degradation was observed up to 91 days at all
10 Temperatures.

Figure 4 shows the results in graphical form.

Example 5:

15

Sodium Hyaluronate 3% + Dexamethosone 1mg/ml + Brilliant Blue FCF(F D & C Blue #1).

20 **Example 6:**

Sodium Hyaluronate 5% + Dexamethasone 2mg/ml + Isosulfan Blue.

25 **Example 7:**

Sodium Hyaluronate 5% + Dexamethasone 2mg/ml + Fluroscien

Example 8:

30

Sodium hyaluronate 3% + Dexamethasone 1mg/ml + polyglycolic acid polymer (dyed)

- 22 -

Example 9:

Sodium Hyaluronate 2% + Nicotinamide Mononucleotide (NMN)

5

Example 10:

Sodium Hyaluronate 3% + Dexamethasone + Nicotinamide
Mononucleotide (NMN)

10

Example 11:

Sodium Hyaluronate 2% + Nicotinamide riboside

15 It is to be understood that, if any prior art publication
is referred to herein, such reference does not constitute
an admission that the publication forms a part of the
common general knowledge in the art, in Australia or any
other country.

20

In the claims which follow and in the preceding
description of the disclosure, except where the context
requires otherwise due to express language or necessary
implication, the word "comprise" or variations such as
25 "comprises" or "comprising" is used in an inclusive sense,
i.e. to specify the presence of the stated features but
not to preclude the presence or addition of further
features in various embodiments of the invention.

- 23 -

Claims:

1. A process of limiting the impact of surgery on a
nerve, the process comprising applying a therapeutic
5 substance to the nerve during surgery.
2. A process as defined in claim 1, wherein the
therapeutic substance is selected from substances
that can intervene in the activation of pathways of
10 cellular degradation within the nerve.
3. A process as defined in claim 1 or 2, wherein the
therapeutic substance comprises an active
pharmacological ingredient and a carrier.
15
4. A process as defined in claim 3, wherein the carrier
is a depot matrix.
5. A process as defined in claim 3 or 4, wherein the
20 carrier is adapted to slow the release of the active
pharmacological ingredient.
6. A process as defined in any one of claims 3 through
5, wherein the carrier has a consistency adapted to
25 reduce dissemination of the active pharmacological
ingredient beyond the site at which its effect is
intended.

- 24 -

7. A process as defined in any one of claims 3 through 6, wherein the carrier is adapted to localise the active pharmacological ingredient to the site at which its effect is intended.

5

8. A process as defined in any one of claims 2 through 5, wherein the active pharmacological ingredient is dexamethasone.

10 9. A process as defined in any of the preceding claims, wherein the step of applying a therapeutic substance to the nerve is performed upon exposure of the nerve during surgery.

15 10. A formulation for reducing nerve trauma comprising an active pharmacological ingredient adapted to intervene in the activation of pathways of cellular degradation within the nerve and a carrier adapted to reduce dissemination of the active
20 pharmacological ingredient beyond the site at which its effect is intended.

11. A formulation as defined in claim 10, wherein the carrier is adapted to slow release of the active
25 pharmacological ingredient.

12. A formulation as defined in claim 10 or 11, wherein the carrier is adapted to localise application of the active pharmacological ingredient
30 to the site of intended effect.

- 25 -

13. A formulation as defined in any one of claims 10
- 12, further comprising a marker.
14. Use of a formulation as defined in any one of
5 claims 10 - 13 during surgery.
15. Use of a formulation as defined in claim 14,
wherein the use comprises applying the formulation to
a nerve that has been exposed during surgery.
- 10 16. A composition comprising hyaluronic acid and
dexamethasone for use in the treatment and protection
of nerves during surgery.
- 15 17. A composition as defined in claim 16, wherein
the hyaluronic acid is in the concentration of
between 1% and 3% w/w.
18. A composition as defined in claim 16, wherein
20 the concentration of hyaluronic acid is between
approximately 10mg/mL and 50mg/mL.
19. A composition as defined in claim 16, wherein
the hyaluronic acid is in the form of sodium
25 hyaluronate with a molecular weight of between
approximately 0.8 and approximately 1.0 MDa.
20. A composition as claimed in claim 19, wherein
the hyaluronic acid has a concentration of
30 approximately 5% w/w.
21. A composition as defined in claim 16, wherein
the hyaluronic acid is in the form of sodium

- 26 -

hyaluronate with a molecular weight of between approximately 2.0 MDa and approximately 2.3 MDa.

22. A composition as claimed in claim 21, wherein
5 the hyaluronic acid has a concentration of approximately 3% w/w.

23. A composition as defined in any one of claims
16 - 22, wherein the dexamethasone is in the form of
10 dexamethasone phosphate.

24. A composition as defined in any one of claims 16
- 23, wherein the dexamethasone has a weight
percentage between 0.5% and 5% w/w.

15 25. A composition as defined in any one of claims 16
- 22, wherein the dexamethasone is in the form of dexamethasone sodium phosphate.

20 26. A composition as defined in claim 25 wherein the dexamethasone sodium phosphate is in the concentration of between 0.1mg/mL and 10.0mg/mL.

25 27. A composition as defined in claim 25 wherein the dexamethasone sodium phosphate is in the concentration of approximately 1 mg/mL.

28. A composition as defined in claim 25 wherein the dexamethasone sodium phosphate is in the
30 concentration of approximately 4 mg/mL.

29. A composition as defined in any one of claims 16
- 28, further comprising one or more of creatinine,

- 27 -

sodium citrate, sodium disulfite, methyl paraben,
propyl paraben.

30. Use of a composition comprising hyaluronic acid
5 and dexamethasone in the manufacture of a medicament
for treatment and protection of nerves during
surgery.

31. A method of delivering a therapeutic substance
10 during surgery, the method comprising:
loading a solid phase biodegradable scaffold with a
therapeutic substance; positioning the scaffold
during surgery such that the therapeutic substance is
delivered to a desired location.

15 32. A method of delivering a therapeutic substance
during surgery, as defined in claim 31, wherein the
therapeutic substance is selected from substances
that can intervene in the activation of pathways of
20 cellular degradation within the nerve.

33. A method of delivering a therapeutic substance
during surgery, as defined in claim 32, wherein the
desired location is proximal to a nerve.

25 34. A method of delivering a therapeutic substance
during surgery, as defined in claim 33, wherein the
step of positioning the scaffold is performed upon
exposure of the nerve during surgery.

30 35. A method of delivering a therapeutic substance
during surgery, as defined in any one of claims 31 -
34, wherein the therapeutic substance is
dexamethasone.

- 28 -

36. A method of delivering a therapeutic substance during surgery, as defined in claim 31, wherein the therapeutic substance comprises a formulation
5 comprising a biodegradable carrier and a therapeutic ingredient advantageous during tonsillectomy or sinus surgery.
37. A method of delivering a therapeutic substance during surgery, as defined in claim 36, wherein the
10 therapeutic ingredient comprises a local anaesthetic.
38. A method of delivering a therapeutic substance during surgery, as defined in claim 36 or 37, wherein
15 the therapeutic ingredient comprises an anti-inflammatory agent.
39. A method of delivering a therapeutic substance during surgery, as defined in any one of claims 36
20 through 38, wherein the therapeutic ingredient comprises an antibiotic.
40. A method of delivering a therapeutic substance during surgery, as defined in any one of claims 36
25 through 39, wherein the therapeutic ingredient comprises a haemostatic agent.
41. A method of delivering a therapeutic substance during surgery, as defined in claim 40, wherein the
30 therapeutic substance comprises a formulation comprising a biodegradable carrier and a therapeutic ingredient advantageous in treatment of burns or skin loss.

- 29 -

42. A method of delivering a therapeutic substance during surgery, as defined in claim 31, wherein the therapeutic substance comprises a formulation comprising a biodegradable carrier and a chemotherapy agent.

43. A system for delivering a therapeutic substance during surgery, the system comprising a solid phase biodegradable scaffold with a therapeutic substance loaded thereon.

44. A system as defined in claim 43, wherein the scaffold further is further loaded with a haemostatic agent.

45. A system as defined in claim 43 or 44, wherein the therapeutic substance is selected from substances that can intervene in the activation of pathways of cellular degradation within the nerve.

46. A system as defined in any one of claims 43 through 45, wherein the therapeutic substance is dexamethasone.

47. A formulation comprising an active pharmacological ingredient having a neuroprotective effect and a carrier adapted to reduce dissemination of the active pharmacological ingredient beyond the site at which its effect is intended.

48. A formulation as defined in claim 47, wherein the active pharmacological ingredient is a corticosteroid.

- 30 -

49. A formulation as defined in claim 47 or 48,
wherein the carrier is a depot matrix.

50. A process of protecting a nerve during surgery,
5 the process comprising identifying a nerve using a
nerve monitor and applying a therapeutic substance to
the nerve.

51. A process as defined in claim 50, further
10 comprising the step of monitoring the nerve function
by monitoring EMG activity from muscles innervated by
the affected nerve.

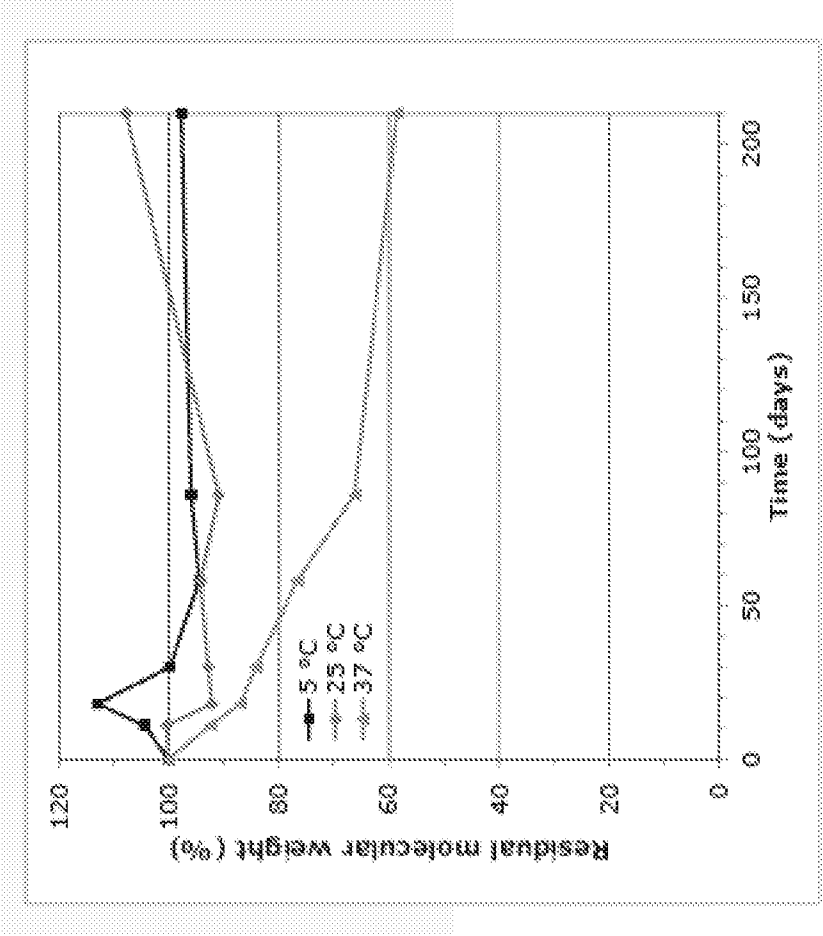


Fig. 1

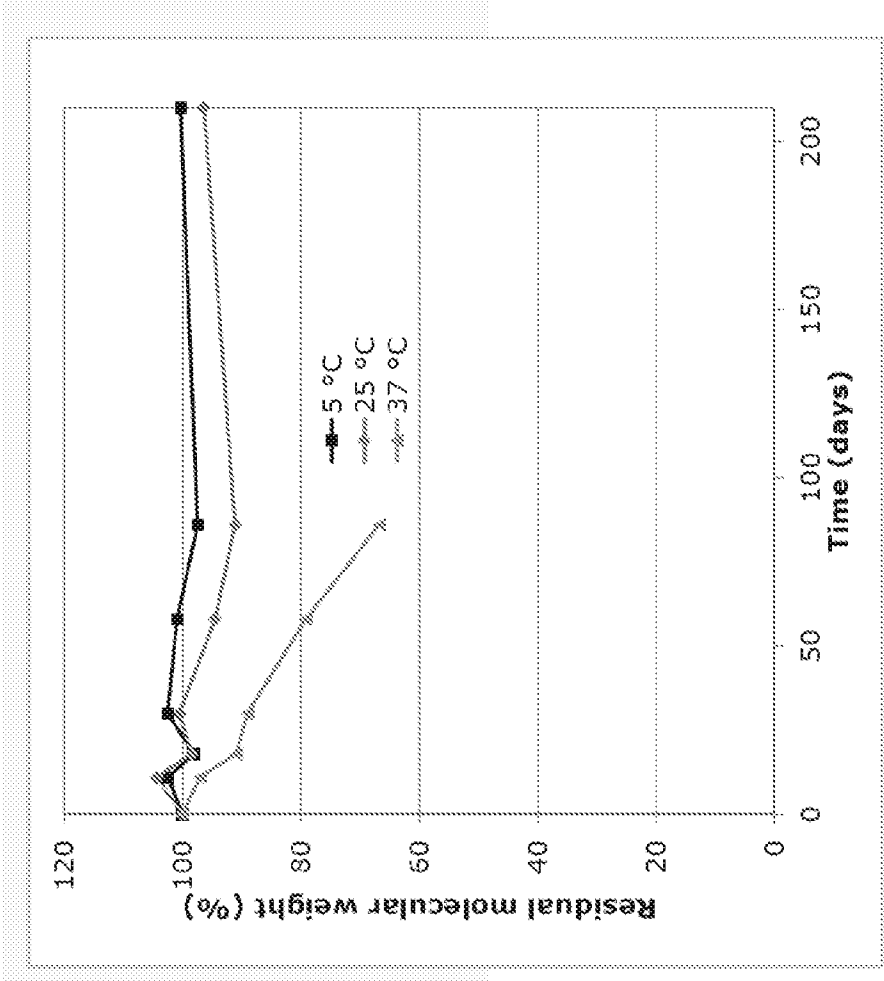


Fig. 2

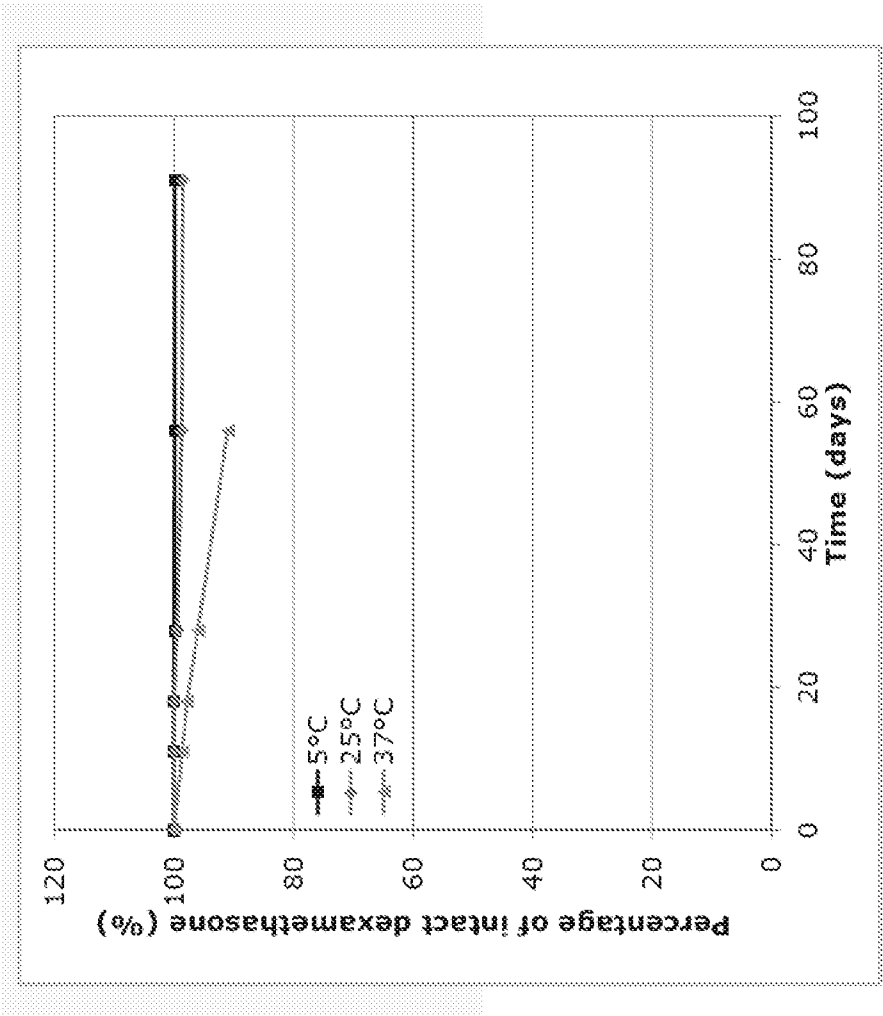


Fig. 3

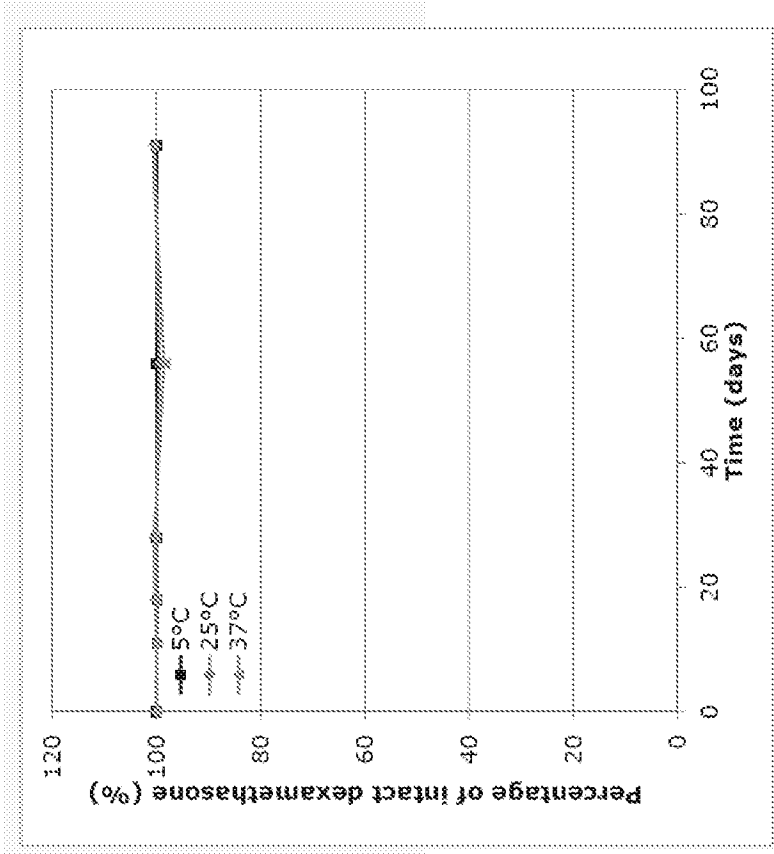


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2016/050445

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/573 (2006.01) A61K 47/36 (2006.01) A61P 41/00 (2006.01) A61K 9/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE and STN: EPODOC, WPIAP, NPL, HCAPLUS, BIOSIS, MEDLINE, EMBASE

nerve, surgery, corticosteroids, dexamethasone, carriers, hyaluronic acid, monitors, EEG/EMG.

Patentscope, AusPat and Non-OPI internal databases: inventor and applicant name searches.

Google: keywords - "nerve trauma, surgery, dexamethasone, hyaluronic acid", "nerve monitors, surgery"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 26 July 2016		Date of mailing of the international search report 26 July 2016	
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au		Authorised officer Joseph Ambrus AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262223649	

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/AU2016/050445
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/0263456 A1 (MCKAY, W) 22 October 2009 [Title]; [Abstract]; [0001]; [0003]; [0008]; [0040-0042]; [0057]; [0064]; [0068]; [0070]; [0108]; [0110]; [0149-0159]; [0160-0169].	1-35, 38, 43 and 45-51
X	WO 2008/157057 A2 (WARSAW ORTHOPEDIC, INC.) 24 December 2008 [Title]; [Abstract]; [Page 3, lines 24-30]; [Page 4, lines 1-18]; [Page 6, lines 15-18]; [Page 19, lines 17-20]; [Page 23, line 22 – Page 24, line 23]; [Page 24, line 30 – Page 25, line 3]; [Page 29, line 7 – Page 30, line 27].	1-35, 38, 43 and 45-51
X	US 8190271 B2 (OVERSTREET, E.H. et al.) 29 May 2012 [Title]; [Abstract]; [Column 1, lines 16-17]; [Column 1, lines 33-36]; [Column 2, lines 58-59]; [Column 3, lines 1-2]; [Column 7, lines 43-48]; [Column 8, lines 6-13]; [Column 13, lines 1-11]; [Column 15, lines 7-30]; [Column 15, lines 31-52]; [Column 18, line 38 – Column 19, line 17].	1-8, 10-14, 31-35, 38, 43 and 45-51
X	US 6238702 B1 (BERDE, C. B. et al.) 29 May 2001 [Abstract]; [Column 3, lines 48-56]; [Column 6, lines 65-67]; [Column 8, lines 39-67]; [Column 20, lines 1-67]; [Column 22, line 62 – Column 23, line 49]; [Column 26, lines 45-53].	1-35, 38, 43 and 45-51
X	WO 2014/116876 A1 (SEMNUR PHARMACEUTICALS, INC.) 31 July 2014 [Title]; [Abstract]; [0002]; [0004]; [0007]; [0029-0030]; [0043]; [0064-0066]; [0067 – Table 1]; [0100]; [0104]; [0108]; [0112]; [0119], [0121 – Table 8].	1-35, 38, 43 and 45-51
X	ITO, T. et al., 'Anti-inflammatory function of an in situ cross-linkable conjugate hydrogel of hyaluronic acid and dexamethasone'. Biomaterials, 2007, vol. 28, issue 10, pages 1778-1786. [Title]; [Page 1778, column 1, paragraph 1]; [Page 1778, column 2, paragraph 1]; [Page 1779, column 1, paragraphs 1-2]; [Page 1779, column 2, section 2.2.4-2.2.5]; [Page 1779, section 2.2.5]; [Page 1781, column 1]; [Page 1782, columns 1-2, section 3.4]; [Pages 1782-1783, section 3.5].	10-13, 16-29, 31-35, 38, 43 and 45-49
X	WO 2002/043785 A2 (OCULEX PHARMACEUTICALS, INC.) 06 June 2002 [Abstract]; [00011]; [00023]; [00036]; [00040]; [00041]; [00060-00084]	10-14, 31-32, 38, 43 and 45-49
X	OZSOY, Z. et al., 'The effect of methylprednisolone and tenoxicam on the protection of damage of the nerve physiormorphology caused by prolene mesh', International Journal of Surgery. 2015, vol. 22, pages 159-163. [Title]; [Page 160, column 1, paragraph 1]; [Page 160, Column 1, “2. Materials and methods”]; [Page 160, Column 2, “2. Materials and methods”]; [Page 161, column 2, paragraph 1]; [Page 163, column 1, “5. Conclusions”].	50-51
Form PCT/ISA/210 (fifth sheet) (July 2009)		

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Supplemental Box**Continuation of: Box III**

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

This Authority has found that there are different inventions based on the following features that separate the claims into distinct groups:

- Claims 1-30 and 50-51 are directed to methods, processes and formulations comprising a therapeutic agent for reducing nerve trauma during surgery. The feature of reducing nerve trauma during surgery is specific to this group of claims.
- Claims 31-46 are directed to a method/system for delivering a therapeutic agent during surgery. The feature of treatments relating to surgery is specific to this group of claims.
- Claims 47-49 are directed to a formulation comprising a neuroprotective agent and a carrier adapted to reduce dissemination beyond the site at which its effect is intended. The feature of a formulation comprising a neuroprotective agent and carrier is specific to this group of claims.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/AU2016/050445	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
US 2009/0263456 A1	22 October 2009	US 2009263456 A1	22 Oct 2009
WO 2008/157057 A2	24 December 2008	WO 2008157057 A2	24 Dec 2008
		CN 101765422 A	30 Jun 2010
		EP 2170271 A2	07 Apr 2010
		JP 2010530435 A	09 Sep 2010
		US 2008317805 A1	25 Dec 2008
		US 2014336162 A1	13 Nov 2014
US 8190271 B2	29 May 2012	US 2009062896 A1	05 Mar 2009
		US 8190271 B2	29 May 2012
		US 2009292237 A1	26 Nov 2009
		US 8271101 B2	18 Sep 2012
		US 2013041331 A1	14 Feb 2013
		US 2013079749 A1	28 Mar 2013
US 6238702 B1	29 May 2001	WO 2009029866 A2	05 Mar 2009
		US 6238702 B1	29 May 2001
		AU 5126993 A	29 Mar 1994
		AU 683022 B2	30 Oct 1997
		AU 5720796 A	21 Nov 1996
		AU 705737 B2	03 Jun 1999
		CA 2144407 A1	17 Mar 1994
		CA 2220180 A1	07 Nov 1996
		EP 0659073 A1	28 Jun 1995
		EP 0659073 B1	19 Dec 2001
		EP 0825853 A1	04 Mar 1998
		EP 0825853 B1	25 Feb 2004
		EP 1132080 A2	12 Sep 2001
		JP H08503695 A	23 Apr 1996
		JP 3007687 B2	07 Feb 2000
		JP H11504634 A	27 Apr 1999
		US 5618563 A	08 Apr 1997
		US 5700485 A	23 Dec 1997
		US 5922340 A	13 Jul 1999
		US 6214387 B1	10 Apr 2001
WO 9405265 A1	17 Mar 1994		

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.
Form PCT/ISA/210 (Family Annex)(July 2009)

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/AU2016/050445	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		WO 9634599 A1	07 Nov 1996
<div>Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.</div> <div>Form PCT/ISA/210 (Family Annex)(July 2009)</div>			

INTERNATIONAL SEARCH REPORT		International application No. PCT/AU2016/050445	
Information on patent family members			
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2014/116876 A1	31 July 2014	WO 2014116876 A1	31 Jul 2014
		AU 2014209346 A1	23 Jul 2015
		CA 2897467 A1	31 Jul 2014
		CN 105073138 A	18 Nov 2015
		EP 2948182 A1	02 Dec 2015
		JP 2016510329 A	07 Apr 2016
		KR 20150114505 A	12 Oct 2015
		MX 2015009455 A	12 Jan 2016
		TW 201442713 A	16 Nov 2014
		US 2014356434 A1	04 Dec 2014
		WO 2002/043785 A2	06 June 2002
AU 3649502 A	11 Jun 2002		
AU 2002236495 B2	11 May 2006		
AU 2006201271 A1	27 Apr 2006		
AU 2006201271 B2	24 Aug 2006		
BR 0115772 A	13 Jan 2004		
CA 2429998 A1	06 Jun 2002		
EP 1339438 A2	03 Sep 2003		
EP 1339438 B1	19 Oct 2005		
EP 1550471 A1	06 Jul 2005		
EP 1621219 A2	01 Feb 2006		
JP 2004210798 A	29 Jul 2004		
JP 2004514702 A	20 May 2004		
JP 2006193532 A	27 Jul 2006		
US 2002182185 A1	05 Dec 2002		
US 6699493 B2	02 Mar 2004		
US 2004137034 A1	15 Jul 2004		
US 7033605 B2	25 Apr 2006		
US 2007190112 A1	16 Aug 2007		
US 7625582 B2	01 Dec 2009		
US 2005249710 A1	10 Nov 2005		
US 7767223 B2	03 Aug 2010		
US 2009062249 A1	05 Mar 2009		
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/AU2016/050445	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		US 7846468 B2	07 Dec 2010
		US 2008050420 A1	28 Feb 2008
		US 8043628 B2	25 Oct 2011
		US 2006198871 A1	07 Sep 2006
		US 8071120 B2	06 Dec 2011
		US 2007298076 A1	27 Dec 2007
		US 8088407 B2	03 Jan 2012
		US 2013274689 A1	17 Oct 2013
		US 8828446 B2	09 Sep 2014
		US 2015005272 A1	01 Jan 2015
		US 9283178 B2	15 Mar 2016
		US 2008050421 A1	28 Feb 2008
		US 2008069859 A1	20 Mar 2008
		US 2012022034 A1	26 Jan 2012
		US 2012059462 A1	08 Mar 2012
		US 2016193230 A1	07 Jul 2016
End of Annex			
<div> Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009) </div>			