New Zealand Datasheet

1 PRODUCT NAME

MOVAPO® Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Apomorphine hydrochloride 10 mg/mL injection solution

3 PHARMACEUTICAL FORM

MOVAPO Injection is a clear, colourless or almost colourless sterile solution for injection, practically free from visible particles with a pH of 3.0 – 4.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MOVAPO Injection is indicated to reduce the number and severity of 'off' phases in patients with Parkinson's disease severely disabled by motor fluctuations refractory to conventional therapy. Initiation of therapy with MOVAPO Injection should be undertaken in a specialist unit in a hospital setting. Conventional therapy should be continued during 'on' phases.

4.2 Dose and method of administration

The optimal dosage of MOVAPO Injection has to be determined on an individual patient basis. Hospital admission under appropriate specialist supervision is advised when establishing a patient's therapeutic regime.

It is essential that the patient is established on the antiemetic domperidone for at least 48 - 72 hours prior to initiation of therapy.

Patient Selection

For patients in whom conventional therapy has failed, MOVAPO Injections are only considered to be suitable for Parkinson's disease patients capable of recognising and anticipating 'off' phases in motor performance. Patients must be capable and motivated for MOVAPO Injection to be used effectively. Adult patients through all age ranges have been successfully managed with apomorphine injections. MOVAPO Injection is not recommended in children and adolescents up to 18 years of age (see section 4.3).

The elderly are well represented in the population of patients with Parkinson's disease and constitute a high proportion of those studied in clinical trials of apomorphine. The management of elderly patients treated with apomorphine has not differed from that of younger patients, except for the extra caution on commencing therapy, because of the risk of postural hypotension.

Patients who have shown a good 'on' period response during the initiation stage of apomorphine therapy, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections, may be commenced on or transferred to continuous subcutaneous infusion by minipump and/or syringe driver.

The practical steps described below should be followed when commencing a patient on

treatment:

- Pre-treat with domperidone.
- Discontinue all existing antiparkinsonian medication to provoke an 'off' phase in motor performance.
- Determine the threshold dose response to MOVAPO Injection that produces an unequivocal motor response.
- Re-establish other antiparkinsonian agents.
- Determine effective treatment regimen for MOVAPO Injection.
- Teach patient and/or carer how and when to administer.
- Discharge from hospital.
- Monitor frequently and adjust dosage regimen as appropriate.
- Full details are given below.

Pre-treatment

Domperidone is a peripherally acting dopamine receptor antagonist given by mouth to prevent nausea and vomiting. Domperidone is commenced 48 - 72 hours prior to the first dose of MOVAPO Injection. When patients are stabilised with respect to dosage of MOVAPO Injection, the dose of domperidone is reduced by 10 mg per day every week until mild nausea appears. The maintenance dose of domperidone is the lowest level which completely prevents nausea. Domperidone can usually be withdrawn after several weeks. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk (see Section 4.4). The cardiovascular assessment should include an ECG and QT measurement. Patients with severe renal insufficiency will require the dosing interval of domperidone to be changed from three times a day to once or twice a day. For further information regarding domperidone refer to the product information and consumer product information.

Provoking and Assessing an 'Off' Phase

After at least 3 days of hospitalisation, all antiparkinsonian therapy is withheld overnight to provoke an 'off' phase in motor performance and to undertake a baseline motor assessment as follows:

(a) Alternate, unilateral hand tapping for 30 seconds on mounted digital counters (preferably 20 cm apart).
(b) Time taken to walk 12 metres.
(c) Clinical assessment of tremor and dyskinesia according to a four point scale (0 = nil, 1 = mild, 2 = moderate, 3 = severe).
(d) Scoring on a modified Webster disability scale to assess 12 features of parkinsonism (maximum disability score of 36).

Determination of the Threshold Dose

Following baseline motor assessment, the patient is challenged for MOVAPO Injection responsiveness according to the following schedule:

- 1.5 mg MOVAPO Injection (0.15 mL) is injected subcutaneously and the patient is observed over 30 minutes for motor responsiveness.
- If no or poor response is obtained, a second dose of 3 mg MOVAPO Injection (0.3 mL) is given 40 minutes after the first dose, and the patient observed for a further 30 minutes.
- The dosage is increased in an incremental fashion every 40 minutes and the patient observed carefully for an unequivocal motor response. The third dose is 5 mg SC, and the fourth dose is 7 mg SC. If the patient shows no response to the 7 mg dose then

the patient must be classified as a non-responder to MOVAPO Injection and no further attempts to provoke a motor response should be made. If the patient shows only a mild response to the 7 mg dose, a maximum dose of 10 mg can be used to see if an unequivocal motor response is possible.

- The lowest dose producing an unequivocal motor response is called the threshold dose. For the majority of patients, the threshold dose is less than 7 mg MOVAPO Injection (0.7 mL), although very occasionally it can be up to 10 mg MOVAPO Injection (1.0 mL).

Motor responsiveness is judged to be positive if 2 or more of the following are seen:
(a) More than 15% increase in tapping score.
(b) More than 25% improvement in walking time.
(c) An improvement of at least 2 points of tremor score.
(d) An improvement of Webster's score of 3 or more.

Initiation of Treatment
Following establishment of an acceptable threshold dose of MOVAPO Injection, the patient should be restarted on conventional antiparkinsonian therapy.

A subcutaneous injection of the established threshold dose may then be given into the lower abdomen or outer thigh at the first signs of an 'off' phase. The patient should then be observed over the following hour and the quality of their 'on' phase noted. It may be appropriate to modify the dose of MOVAPO Injection according to the patient's response.

Close monitoring of therapeutic benefits and adverse reactions under specialist supervision is required after initiation of treatment.

MOVAPO Injection is administered by the subcutaneous route, either by intermittent injection or continuous infusion. Intermittent injection is either into the anterior abdominal wall or anterolateral thigh. The usual dosage range is 2.4 to 3.6 mg per injection; the maximum single dose being 6 mg and the maximum total daily dose being 50 mg.

To ensure accurate dosing, 1.0 mL insulin syringes should be used to administer intermittent injections. The intermittent injection is given in an undiluted form. For microbiological reasons, the contents of a syringe used for intermittent injections should be used within 24 hours of filling. Store in a refrigerator at 2 to 8°C between injections. Any solution remaining at the end of the day should be discarded and not reused on the following day.

Patients who have shown a good 'on' phase response during the initiation stage, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (e.g. 8-10 injections per day), may be commenced on or transferred to continuous subcutaneous infusion by minipump.

Continuous subcutaneous infusion of MOVAPO Injection is effected via administration by portable syringe driven pump at a minimum dilution of 1:1 with sodium chloride 0.9% (normal saline). The dose should be titrated to the patient's response. Infusion rates can be commenced at 1 mg/hr, and then increased as necessary. The maximum daily dose should in general not exceed 200 mg/day. In clinical studies the required infusion rate varies between 1.25 and 5.5 mg/hr (equivalent to 0.02 and 0.08 mg/kg/hr), with most patients requiring (a total of) between 2 and 4 mg/hr.

Infusions should be run for waking hours only. Unless the patient is experiencing night time problems, 24 hour infusions are not advised. The infusion site should be changed every 12 hours. Prolonged infusion times are associated with local adverse effects to a more severe degree.

Monitoring Treatment
Long term specialist supervision of patients is advised.

There is a high probability of adverse effects to MOVAPO Injection therapy. The frequency and severity of adverse events should be monitored carefully at regular intervals and a reassessment of the patient carried out if appropriate. Adjustments to the dosage or discontinuation may be necessary.

4.3 Contraindications

MOVAPO Injection is contraindicated in patients with a known hypersensitivity or allergy to apomorphine, morphine or chemically related products.

MOVAPO Injection should not be administered to patients with pre-existing neuropsychiatric problems or dementias due to either pathological processes, e.g. Alzheimer's disease, or to patients whose 'on' response to L-dopa is marred by severe dyskinesia, hypotonia or psychotoxicity.

MOVAPO Injection is also contraindicated in patients with inadequate renal or liver function, unstable coronary vascular disease, cerebrovascular disease, respiratory depression or CNS depression.

MOVAPO is contraindicated for children and adolescents under 18 years of age.

MOVAPO Injection is also contraindicated in patients with a known hypersensitivity to sodium metabisulfite.

4.4 Special warnings and precautions for use

For subcutaneous use only (see Section 4.8).

Patients sensitive to morphine or its derivatives may be sensitive to MOVAPO. MOVAPO should therefore not be administered to patients with a known hypersensitivity or allergy to apomorphine, morphine or chemically related compounds (see Section 4.3).

MOVAPO contains sodium metabisulfite which may cause allergic type reactions, including anaphylactic symptoms and life threatening or less severe asthmatic episodes in susceptible people (see Section 4.3).

In patients with cardiac decompensation or cerebrovascular disease, vomiting may cause an increase in blood pressure that may lead to haemorrhage and vascular accidents. Apomorphine is therefore contraindicated in these patients (see Section 4.3).

Caution should be used in administering MOVAPO to patients with a predisposition to nausea and vomiting. Apomorphine may cause an increased risk of persistent vomiting. A risk-benefit assessment should be considered in these patients.

Since apomorphine may produce hypotension, even when given with domperidone pre-treatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with pre-existing postural hypotension.

When used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also, medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed.

Monitoring for an effect on the QTc interval is advisable. An ECG should be performed:

- prior to treatment with domperidone
- during the treatment initiation phase
- as clinically indicated thereafter

The patient should be instructed to report possible cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy. At each medical visit, risk factors should be revisited.

Apomorphine is associated with local subcutaneous effects. These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) in order to avoid areas of nodularity and induration.

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine.

Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range (see Section 4.5).

Neuropsychiatric problems co-exist in many patients with advanced Parkinson's disease. There is evidence that for some patients, neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients. Apomorphine has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage may be considered.

The use of apomorphine in conjunction with levodopa treatment may cause Coombs' positive haemolytic anaemia. An initial screen prior to commencement of treatment and at 6 monthly intervals is recommended. In the event of the development of a haemolytic anaemia, a haematological specialist should be consulted. The dose of apomorphine and/or levodopa should be reduced, with careful monitoring of the patient's motor state. It may be necessary to discontinue treatment with levodopa and/or apomorphine in the event that it is not possible to control the anaemia satisfactorily.

MOVAPO Injection should be used with caution in patients with endocrine, renal, pulmonary or cardiovascular disease.

Periodic evaluation of hepatic, haemopoietic, renal and cardiovascular function is advised.

Patients with severe renal insufficiency may require the dosing interval for domperidone to be less frequent (see Section 4.2, Pre-treatment).

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including MOVAPO Injection. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Dopamine dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with apomorphine. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

Use in debilitated patients
Extra caution is also recommended in debilitated patients, since they may show an increased susceptibility or be more sensitive to the respiratory depressant effects of apomorphine.

Use in the elderly
Extra caution is also recommended in geriatric patients, since they may show an increased susceptibility or be more sensitive to the respiratory depressant effects of apomorphine. Extra caution is recommended during initiation of therapy in elderly patients because of the risk of postural hypotension.

Paediatric use
MOVAPO is contraindicated for children and adolescents under 18 years of age.

Effects on laboratory tests
Positive Coombs' tests have been reported for patients receiving apomorphine.

4.5 Interaction with other medicines and other forms of interaction

Patients selected for treatment with apomorphine HCl are almost certain to be taking concomitant medications for their Parkinson’s disease. In the initial stages of apomorphine HCl therapy, the patient should be monitored for unusual side-effects or signs of potentiation of effect.

Drugs which interfere with central amine mechanisms such as tetrabenazine, metoclopramide, antipsychotic dopamine blocking agents (such as phenothiazines, thioxanthines and butyrophenones), amphetamines and papaverine should be avoided. If their administration is considered essential, extreme care should be taken and the patient monitored for signs of potentiation, antagonism or other interactions and for any unusual adverse effects.

Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. There

is a potential interaction between clozapine and apomorphine.

The possible side effects of apomorphine on the plasma concentrations of other medicinal products have not yet been studied. Therefore, caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.

Antihypertensive and Cardiac Active Medicinal Products
Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of antihypertensive and cardiac active medicinal products.

It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy
The safety of using apomorphine during pregnancy has not been established in either human or animal studies. MOVAPO should therefore not be used in pregnant women, or those likely to become pregnant.

MOVAPO Injection should not be used during pregnancy unless clearly necessary.

Breast feeding
It is not known whether MOVAPO Injection is excreted in breast milk, although problems in humans have not been documented. Nevertheless, because many drugs are excreted in human milk and because of the potential for serious adverse drug reactions due to apomorphine in breastfed infants, a decision should be made either to discontinue breastfeeding or the drug, taking into account the importance of the drug to the mother.

Effects on Fertility
In a fertility study in male rats, fertility was decreased at 2 mg/kg/day SC, one tenth that of the maximum recommended human dose (based on body surface area). Effects on female fertility have not been determined.

4.7 Effects on ability to drive and use machines

Apomorphine HCl has minor or moderate influence on the ability to drive and use machines.

Patients being treated with apomorphine and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved (see Section 4.4)

4.8 Undesirable effects

Very common (>10%)
Itchy nodular lesions at the injection site may be severe in patients on continuous subcutaneous infusions of MOVAPO injection. Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration (see Section 4.4 Special warnings and precautions for use), erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising, fibrosis and pain) may also occur (see Section 4.4). Care should be taken to ensure that areas of ulceration do not become infected.

Hallucinations have been reported.

Common (1-10%)
Gastrointestinal side effects including nausea and vomiting appear to be the most prevalent adverse effects, however tolerance to these effects develops rapidly. Pre-treatment with domperidone may reduce or prevent these effects (see Section 4.2).

Apomorphine is associated with somnolence. Drowsiness and sedation occur in most patients on initial treatment but these effects largely subside with repeated dosing, although in some patients these effects may persist. Tachyphylaxis to postural related faintness or syncope also occurs rapidly.

Neuropsychiatric disturbances (including confusion and visual hallucinations) have occurred during apomorphine therapy.

Yawning has been reported during apomorphine therapy.

Uncommon (0.1- 1%)
Apomorphine may induce dyskinesias during 'on' periods, which can be severe in some cases, and in a few patients may result in cessation of therapy. Apomorphine has been associated with sudden sleep onset episodes (see Section 4.4).

Postural hypotension is seen infrequently and is usually transient (see Section 4.4).

Breathing difficulties have been reported.

Local and generalised rashes have been reported. Injection site necrosis and ulceration have been reported.

Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine.

Rare (0.01 – 0.1%)
Eosinophilia has rarely occurred during treatment with apomorphine. Peripheral blood eosinophilia, elevated by up to 10%, has occurred in patients on continuous subcutaneous infusion of apomorphine. Blood counts returned to normal in about half of the patients who received treatment over one year.

Due to the presence of sodium metabisulfite, allergic reactions (including anaphylaxis and bronchospasm) may occur.

Not known (cannot be estimated from available data)
Impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine (see Section 4.4).

Aggression and agitation have also been reported.

Headache has been reported.

Peripheral oedema has been reported.

Other adverse reactions to apomorphine that have been reported infrequently include transient rises in serum prolactin, stomatitis, transient metallic taste, rhinorrhoea, increased lacrimation, reduced facial hair growth, loss of libido and spontaneous penile erection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

There is little clinical experience of overdose with apomorphine by this route of administration.
The clinical features of overdose of MOVAPO are an extension of the pharmacological effects of the drug. They include nausea and persistent vomiting, dyskinesias, hypotension and acute circulatory failure, cardiac arrest, respiratory depression, drowsiness and central nervous system depression or stimulation, euphoria, restlessness and hallucinations and possibly coma and death. Concomitant use of domperidone may exacerbate the clinical features of overdose.

An opioid antagonist such as naloxone may be given to treat excessive vomiting, central nervous system depression and respiratory depression due to MOVAPO overdose. Excessive vomiting may also be treated with domperidone. Atropine may be also used to treat bradycardia. To treat hypotension, appropriate measures should be taken e.g. raising the foot of the bed.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists, ATC Classification: N04B C07

Apomorphine is a directly acting dopamine receptor agonist, structurally related to dopamine. Apomorphine has high *in vitro* binding affinity for the dopamine D_4 and D_5 receptor (K_i:4 and 14 nM respectively), moderate affinity (K_i: 26 to 130 nM) for the dopamine D_2 and D_3, adrenergic α_{1D}, α_{2B}, α_{2C} receptors, serotonin $5HT_{1A}$, $5HT_{2A}$, $5HT_{2B}$, and $5HT_{2C}$ receptors and low affinity for the dopamine D_1 receptor (K_i: 370 nM). Apomorphine exhibits no affinity for the adrenergic β_1 and β_2 or histamine H_1 receptors.

The effect of apomorphine as an antiparkinsonian agent is believed to be the result of direct stimulation of postsynaptic D2 dopamine receptors, but stimulation of presynaptic D2 dopamine receptors and antagonism of α2 adrenergic receptors may also be important. Apomorphine reduces the tremor, rigidity and bradykinesia in patients receiving levodopa. Apomorphine induces vomiting by direct stimulation of the medullary chemoreceptor trigger zone.

5.2 Pharmacokinetic properties

The peripheral pharmacokinetics of apomorphine have been studied following subcutaneous injection, subcutaneous infusion and intravenous infusion.

Absorption
Following intramuscular or subcutaneous administration, apomorphine is reported to be well absorbed. Peak plasma concentration occurs as early as three minutes following subcutaneous bolus injection. The rapid and complete absorption from subcutaneous tissues and rapid clearance is believed to correlate with the rapid onset and brief duration of action respectively. Antiparkinsonian effects are observed within five minutes following subcutaneous bolus administration.

Distribution
The distribution half-life of apomorphine was found to be five minutes. The volume of distribution, plasma clearance and half-life were similar for subcutaneous injection, subcutaneous infusion and intravenous infusion.

Apomorphine reaches a concentration in the brain up to eight times higher than that in plasma, due to high lipid solubility which allows rapid equilibration between blood and tissue compartments.

Metabolism
Apomorphine is metabolised in the liver. Routes of metabolism in humans include sulfation, N-demethylation, glucuronidation and oxidation to norapomorphine by CYP 2B6, CYP 2C8 and CYP 3A4. The major metabolite in humans after sublingual administration was apomorphine sulfate.

Excretion
Apomorphine is cleared rapidly. The elimination half-life ($t_{½}$) is about 33 minutes.

5.3 Preclinical safety data
In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. Apomorphine was not genotoxic *in* vivo in a mouse micronucleus test or in a rat unscheduled DNA synthesis test.

No carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Water for Injections BP. Sodium metabisulfite 1 mg/mL is included in the formulation as an antioxidant.

6.2 Incompatibilities
In the absence of compatibility studies, this product must not be mixed with other medicinal products.

6.3 Shelf life
Shelf life is 36 months (3 years) from manufacture.
Once opened, use immediately. Discard any unused contents.

6.4 Special precautions for storage
Store the 2 mL and 5 mL ampoules below 25°C (Do not freeze). Protect from light.

6.5 Nature and contents of container

MOVAPO® Injection in ampoules contains apomorphine hydrochloride 20 mg in 2mL or 50 mg in 5 mL. The container material is a Type 1 clear glass.

Each ampoule is partially scored with a coloured spot positioned directly above the short score mark. This score mark indicates the breaking point of the ampoule.

Strength	**Pack**
20 mg/2 mL	5 × 2 mL ampoules
50 mg/5 mL	5 × 5 mL ampoules

6.6 Special precautions for disposal

Do not use if the solution has turned green.

The solution should be inspected visually prior to use. Only clear and colourless solutions should be used.

For single use only. Any unused solution should be discarded.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Australian Sponsor:
STADA Pharmaceuticals Australia Pty Ltd
Suite 1101, 46 Market Street
Sydney NSW 2000
Australia

New Zealand Sponsor:
CARSL Consulting
Clinical and Regulatory Services
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PO Box 766 Hastings
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Phone: 0800 581 531

9 DATE OF FIRST APPROVAL

11 May 1995

10 DATE OF REVISION OF THE TEXT

24 September 2019

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Additional clarification on the use in elderly patients Possible use by minipump or syringe driver added Review of pre-treatment risk factors added
4.3	Contraindication for children and adolescents under 18 years of age added
4.4	Section updated Use in debilitated patients, use in the elderly, paediatric use and effects on laboratory tests added
4.5	Section updated
4.6	Pregnancy information updated
	Lactation information updated
	Effects on fertility added
4.8	Entire section is updated
4.9	Entire section is updated
5.1	Entire section is updated
5.2	Entire section is updated
5.3	Repeat dose subcutaneous toxicity study information and reproduction information removed.
8	Sponsor details updated