Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Ondansetron 2 mg/ml Solution for Injection

(Ondansetron hydrochloride dihydrate)

UK Licence Number: PL 43801/0001

Sciecure Pharma Limited.

LAY SUMMARY

Ondansetron 2 mg/ml Solution for Injection
(ondansetron hydrochloride dihydrate)

This is a summary of the Public Assessment Report (PAR) for Ondansetron 2 mg/ml Solution for Injection (PL 43801/0001). It explains how for Ondansetron 2 mg/ml Solution for Injection (PL 43801/0001) was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Ondansetron 2 mg/ml Solution for Injection.

The product will be referred to as Ondansetron Solution for Injection throughout the remainder of this public assessment report (PAR).

For practical information about using Ondansetron Solution for Injection patients should read the package leaflet or contact their doctor or pharmacist.

What is Ondansetron Solution for Injection and what is it used for?
Ondansetron Solution for Injection is a 'generic medicine'. This means that Ondansetron Solution for Injection is similar to a 'reference medicine' already authorised in the European Union (EU) called Zofran Injection 2 mg/ml / Zofran Flexi-amp Injection 2 mg/ml (Novartis Pharmaceuticals UK Limited). The reference product may be referred to as Zofran Injection 2 mg/ml throughout the remainder of this PAR.

This product is used for:

- Preventing nausea and vomiting caused by chemotherapy (in adults and children) or radiotherapy for cancer (adults only).
- Preventing nausea and vomiting after surgery.

How does Ondansetron Solution for Injection work?
Ondansetron Solution for Injection contains the active ingredient ondansetron (as hydrochloride dihydrate) which belongs to a group of medicines called anti-emetics. Ondansetron blocks the actions of chemicals in the body that can trigger nausea and vomiting.

How is Ondansetron Solution for Injection used?
The pharmaceutical form of this medicine is a solution for injection. Ondansetron Solution for Injection is normally given by a nurse or doctor. The dose the patient has been prescribed will depend on the treatment they are having.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Ondansetron Solution for Injection have been shown in studies?
No additional clinical studies were needed as Ondansetron Solution for Injection is a generic medicine that is given as an aqueous solution by injection and contains the same active substance in the same concentration as the reference medicine Zofran Injection 2 mg/ml (Novartis Pharmaceuticals UK Limited).

What are the possible side effects of Ondansetron Solution for Injection
Because Ondansetron Solution for Injection is a generic medicine, its benefits and possible side effects are taken as being the same as for the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Ondansetron Solution for Injection, see section 4 of the package leaflet available on the MHRA website.

Why was Ondansetron Solution for Injection approved?
It was concluded that, in accordance with EU requirements, Ondansetron Solution for Injection has been shown to be comparable to Zofran Injection 2 mg/ml (Novartis Pharmaceuticals UK Limited). Therefore, the MHRA decided that, as for Zofran Injection 2 mg/ml (Novartis Pharmaceuticals UK Limited), the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Ondansetron Solution for Injection?
A risk management plan (RMP) has been developed to ensure that Ondansetron Solution for Injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Ondansetron Solution for Injection including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Ondansetron Solution for Injection
A Marketing Authorisation was granted in the UK on 21 August 2018.

The full PAR for Ondansetron Solution for Injection follows this summary.

For more information about treatment with Ondansetron Solution for Injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Sciecure Pharma Limited a marketing authorisation for the medicinal product Ondansetron Solution for Injection (PL 43801/0001) on 21 August 2018. The product is a prescription only medicine (POM) indicated for the management of:

- nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV) in adults.
- chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of post-operative nausea and vomiting (PONV) in children aged ≥ 1 month.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Zofran Injection 2 mg/ml which was first authorised to the marketing authorisation holder (MAH) Glaxo Operations UK Limited (PL 00004/0375) on 07 March 1990 and subsequently underwent a change of ownership procedure to the current MAH, Novartis Pharmaceuticals UK Limited (PL 00101/0985) on 01 October 2015.

Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-hydroxytryptamine (5HT) in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of $5HT_3$ receptors on neurons located both in the peripheral and central nervous system.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous solutions at the time of administration by injection.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Ondansetron Solution for Injection outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

Each ml of solution contains 2 mg of ondansetron (as ondansetron hydrochloride dihydrate).

Ondansetron 4 mg / 2 ml Solution for Injection:
Each 2 ml glass ampoule contains 4 mg of ondansetron (as ondansetron hydrochloride dihydrate).

Ondansetron 8 mg / 4 ml Solution for Injection:
Each 5 ml glass ampoule contains 8 mg of ondansetron (as ondansetron hydrochloride dihydrate).

Other ingredients consist of the pharmaceutical excipients, citric acid monohydrate, sodium citrate, sodium chloride and water for injections.

The finished product is presented in type I clear glass 2 ml ampoules, each containing 2ml of solution or type I clear glass 5 ml ampoules, each containing 4ml of solution. The ampoules are supplied in cartons containing 5 or 10 ampoules.

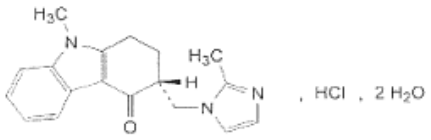
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2. Drug Substance

INN: Ondansetron hydrochloride dihydrate

Chemical name: (1) 4H-Carbazol-4-one, I, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1 H-imidazol-l-yl) methyl]-, monohydrochloride, (±)-, dihydrate;
(2) (±)-2, 3-Dihydro-9-methyl-3-[(2-methylimidazol-l-yl) methyl] carbazol-4(I H)-one monohydrochloride dihydrate

Structural formula:



Molecular formula: $C_{18}H_{19}N_3O.HCl.2H_2O$

Molecular mass: 365.9 g/mol

Appearance: White or almost white powder.

Solubility: Sparingly soluble in water; soluble in methanol; slightly soluble in ethanol; practically insoluble in methylene chloride.

Ondansetron hydrochloride dihydrate is the subject of a European Pharmacopoeia monograph,

All aspects of the manufacture and control of the active substance are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious clear, colourless, sterile solution for injection containing 2 mg ondansetron (as ondansetron hydrochloride dihydrate) per ml of solution that is comparable to the originator product Zofran Injection 2 mg/ml (Novartis Pharmaceuticals UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

This product contains no materials of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specifications
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data that comply with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Products
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years for the unopened ampoule with the storage conditions 'Do not store above 25°C. Store in the original package. Protect from light.'

Injection:
After first opening the medicinal product should be used immediately.

Infusion:
Chemical and physical in-use stability has been demonstrated for 5 days at 25°C and 2-8°C, when the product is diluted to a concentration of 0.32 or 0.64 mg/ml and stored in the original plastic containers of the infusion fluids.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ondansetron hydrochloride dihydrate are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The Applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Ondansetron Solution for Injection is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
According to the regulatory requirements of the CHMP guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) a bioequivalence study is not required for parenteral aqueous solutions and the applicant has not submitted results of a study.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of Ondansetron Solution for Injection.

Based on the data provided, Ondansetron Solution for Injection can be considered a generic of Zofran Injection 2 mg/ml (Novartis Pharmaceuticals UK Limited).

IV.2 Pharmacokinetics
In line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as a parenteral aqueous solution containing the same qualitative and quantitative composition in terms of active substance and excipients and is of the same pharmaceutical form as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted, and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ondansetron Solution for Injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary of safety concerns	
Important identified risks	• Hypersensitivity • Interaction with apomorphine • ECG changes (QTc prolongation) • Hepatic impairment
Important potential risks	• Use in breast-feeding
Missing information	• Use in pregnancy • Use in prevention of delayed or prolonged chemotherapy-induced nausea and vomiting (CINV) • Use for radiotherapy-induced nausea and vomiting in children • Post-operative nausea and vomiting (PONV) in children

Routine pharmacovigilance and risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

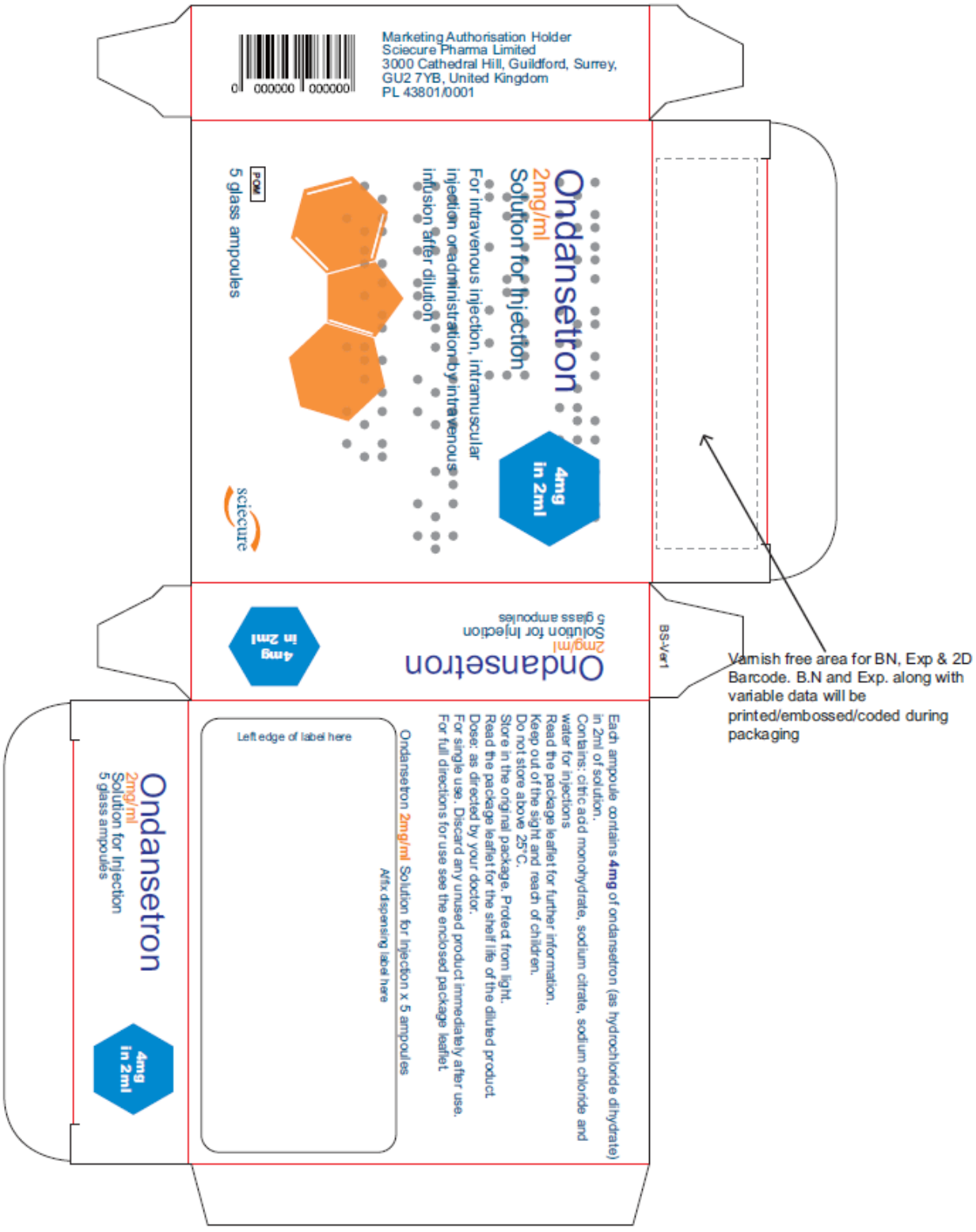
VI Overall conclusion, benefit/risk assessment and recommendation

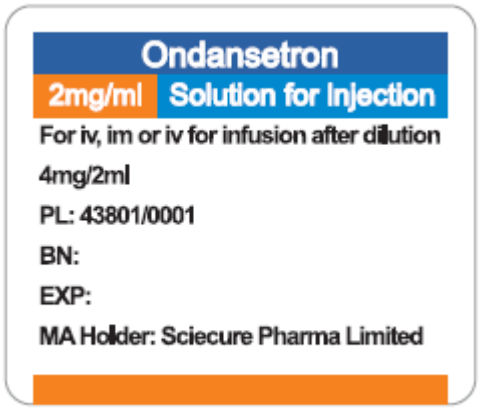
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ondansetron hydrochloride dihydrate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

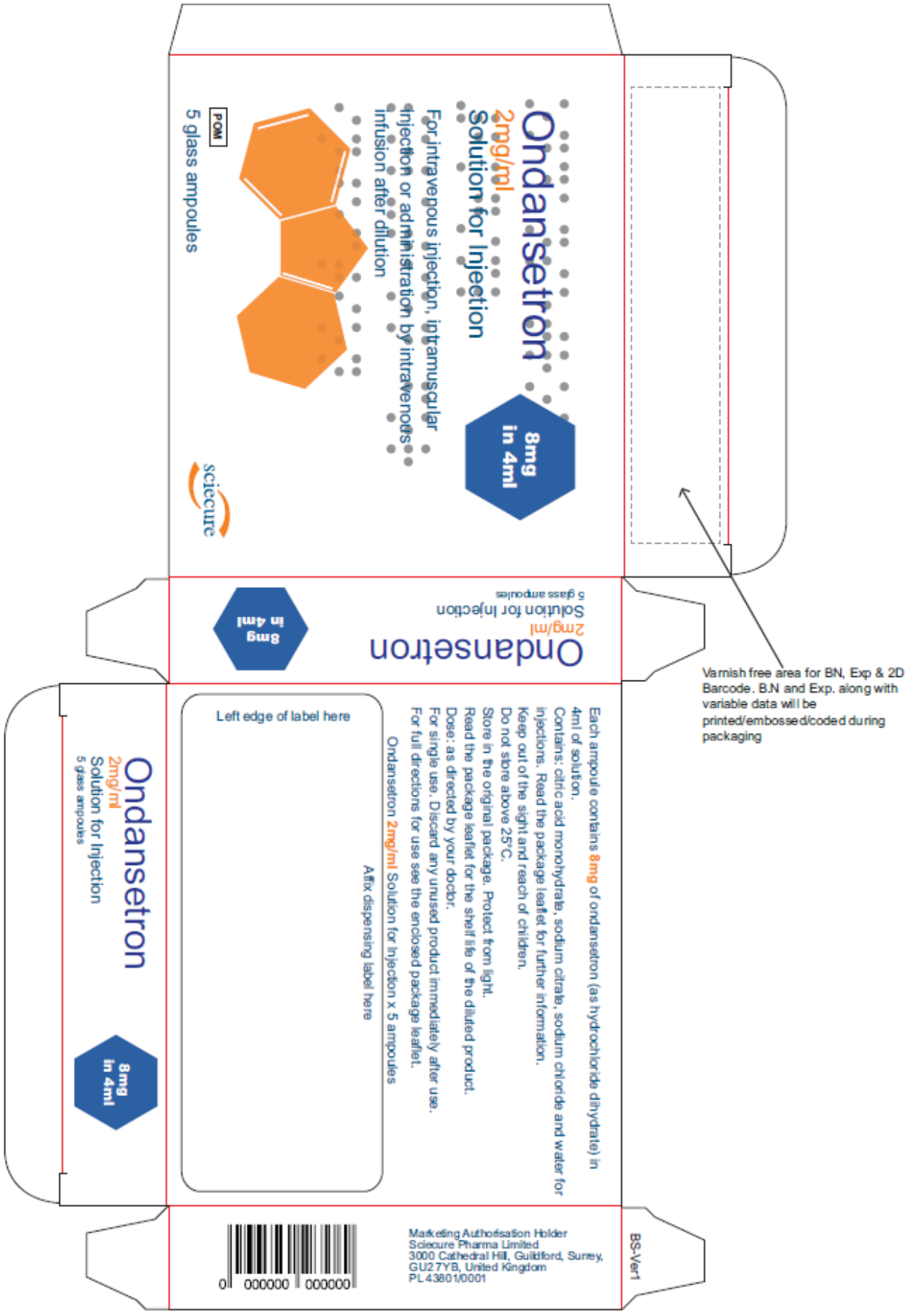
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

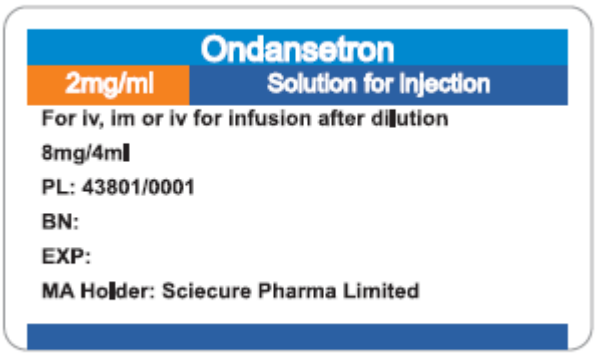
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:




Ondansetron
2mg/ml
Solution for Injection
For iv, im or iv for infusion after dilution
4mg/2ml
PL: 43801/0001
BN:
EXP:
MA Holder: Sciecure Pharma Limited


Ondansetron
2mg/ml
Solution for Injection
8mg in 4ml
For intravenous injection, intramuscular injection or administration by intravenous infusion after dilution
POM
5 glass ampoules
sciecure
Ondansetron
2mg/ml
Solution for Injection
5 glass ampoules
8mg in 4ml
Each ampoule contains 8mg of ondansetron (as hydrochloride dihydrate) in 4ml of solution.
Contains: citric acid monohydrate, sodium citrate, sodium chloride and water for injections. Read the package leaflet for further information.
Keep out of the sight and reach of children.
Do not store above 25°C.
Store in the original package. Protect from light.
Read the package leaflet for the shelf life of the diluted product.
Dose: as directed by your doctor.
For single use. Discard any unused product immediately after use.
For full directions for use see the enclosed package leaflet.
Ondansetron 2mg/ml Solution for Injection x 5 ampoules
Affix dispensing label here
Left edge of label here
Ondansetron
2mg/ml
Solution for Injection
5 glass ampoules
8mg in 4ml
0 000000 000000
Marketing Authorisation Holder
Sciecure Pharma Limited
3000 Cathedral Hill, Guildford, Surrey,
GU2 7YB, United Kingdom
PL 43801/0001
BS-Ver1
Varnish free area for BN, Exp & 2D Barcode. B.N and Exp. along with variable data will be printed/embossed/coded during packaging


Ondansetron
2mg/ml
Solution for injection
For iv, im or iv for infusion after dilution
8mg/4ml
PL: 43801/0001
BN:
EXP:
MA Holder: Sciecure Pharma Limited

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Date submitted	Application type	Scope	Outcome