16 February 2012
EMA/228344/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sancuso

International non-proprietary name: **granisetron**

Procedure No. **EMEA/H/C/002296**

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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List of abbreviations

5-HT_3, (5-HT3)	5-hydroxytryptamine type-3
5-HT_3-RA, (5-HT3-RA)	5-HT3 receptor antagonist
8/C (15/C, X/C)	Study 392MD/***8***/C; Study 392MD/***15***/C; Study 392MD/***X***/C
ADR	Adverse drug reaction
AE	Adverse event
ASCO	American Society for Clinical Oncology
AUC	Area under the (plasma/whole blood) concentration versus time curve
$AUC_{0\text{-inf}}$ (AUC_{inf})	AUC from time 0 and extrapolated to infinity
$AUC_{0\text{-n}}$(AUC_n)	AUC from time 0 to Dn
CC	Complete Control
CI	Confidence Intervals
CINV	Chemotherapy-induced nausea and vomiting
CL	Clearance
C_{max}	Maximum observed concentration
CR	Complete Response
CS	Corticosteroids
CSR	Complete Study Report
D1 (Dn)	D1 (Dn)
ECOG	Eastern Cooperative Oncology Group
Ef (E)	Efficacy
E-R (E-R-A)	Exposure-Response (Exposure response analysis)
EP (PEP, SEP)	Endpoints (Primary EP, Secondary EP)\
ESMO	European Society for Medical Oncology
FAS	Full analysis set
GFR (cGFR, mGFR)	Glomerular Filtration Rate (calculated GFR, measured GFR)
GORD	Gastro Oesophageal Reflux Disease
GTDS	Granisetron Transdermal Delivery System
h (hrs)	Hour (hours)
HE (HEC)	Highly emetogenic (HE chemotherapy)
ITT	Intent to treat population (randomised and transplanted)
IV	Intravenous
M1 (Mn)	M1 (Mn)
ME (MEC)	Moderately emetogenic (ME chemotherapy)
NI	Non-inferiority
NK_1	Neurokinin-1
PD	Pharmacodynamics
PEP	Primary endpoint
PK	Pharmacokinetics
PPK	Population pharmacokinetic
PPP (PPS)	Per-Protocol population (Per-Protocol Set)
RMP	Risk Management Plan
Rx	Treatment
SA (SAWP)	Scientific advise (SAWP)
SAE(s)	Serious adverse event(s)
SEP	Secondary endpoint
Sf (S)	Safety
SPC (SmPC)	Summary of Product Characteristics
Study x/C	Study 392MD/***X***/C
T1/2	Terminal phase half-life
TDS	Transdermal Delivery System
Vd(Vss)	Apparent volume of distribution (at steady-state)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ProStrakan Ltd submitted on 29 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sancuso, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No. 726/2004 – 'Significant innovation or interest of patients at Community level'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 March 2010.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant initially applied for the following indication "prevention of nausea and vomiting in patients receiving moderatly or highly emetogenic chemotherapy". The agreed indication is "SANCUSO transdermal patch is indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy, for a planned duration of 3 to 5 consecutive days, where oral anti-emetic administration is complicated by factors making swallowing difficult.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, comparative bioavailability data with the reference medicinal product Kytril and appropriate non-clinical and clinical data.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Not applicable.

Information on the reference product

The chosen reference medicinal product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
    - Product name, strength, pharmaceutical form: Kytril 1mg Tablets
    - Marketing authorisation holder: Roche Products Limited
    - Date of authorisation: 04-01-1994
    - Marketing authorisation granted by:

      - Member State (EEA): United Kingdom

      - National procedure

- Marketing authorisation number: PL 00031/0591

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Kytril 1mg Tablets
  - Marketing authorisation holder: Roche Products Limited
  - Date of authorisation: 04-01-1994
  - Marketing authorisation granted by:
    - Member State (EEA): United Kingdom
    - National procedure
    - Marketing authorisation number: PL 00031/0591

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Sancuso has been given a Marketing Authorisation in United States of America on 12-09-2008, Korea on 24-12-2008, Philippines on 08-07-2010, Thailand on 20-04-2009, Australia on 02-09-2009 and Kuwait on 17-06-2010.

The medicinal product was refused a license in Austria, Belgium, Bulgaria, Czech Republic, Germany, Greece, Spain, Finland, France, Ireland, Luxemburg, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic and United Kingdom on 05-10-2008 following a Decentralised Procedure.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

PHARBIL Waltrop GmbH

Im Wirrigen 25

D-45731 Waltrop

Germany

Manufacturer responsible for import and batch release in the European Economic Area

PHARBIL Waltrop GmbH

Im Wirrigen 25

D-45731 Waltrop

Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Romaldas Maciulaitis
Co-Rapporteur:	Pieter Neels

- The application was received by the EMA on 29 September 2010.
- The procedure started on 17 November 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 04 February 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 04 February 2011
- During the meeting on 14-17 March 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 05 September 2011.
- During the CHMP meeting on 19-22 September 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 December 2011.
- During the CHMP meeting on 16-19 January, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 13-16 February 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sancuso on 16 February 2012.

2. Scientific discussion

2.1. Introduction

Nausea and vomiting are recognized as 2 of the most upsetting adverse reactions of cancer chemotherapy. Current guidelines propose 5-HT_3 receptor antagonists as an effective pharmacological intervention for prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) with some reservations according to the intensity and duration of chemotherapy. The active substance of SANCUSO 3.1 mg/24 hrs transdermal patch submitted for marketing authorisation is granisetron, a selective 5-HT3 receptor antagonist.

The legal basis for this marketing authorisation application for SANCUSO 3.1 mg/24 h transdermal patch is Article 10(3) ("hybrid application") of Directive 2001/83/EC. The nonclinical and clinical development strategies were therefore designed to bridge to the previous findings of efficacy and safety for the reference product, Kytril (granisetron hydrochloride) 1 mg Tablets. Oral as well as intravenous formulations of granisetron have been authorized and marketed in the EU Member States. The literature has also been reviewed for new information generated since the licensing of the existing dosage forms of granisetron and it has been incorporated in the submitted dossier.

The granisetron transdermal delivery system (granisetron TDS) that is applied in this application has been developed for the prevention of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy for up to 5 consecutive days with an expectation that a single application of the patch offers steady, sustained delivery of granisetron.

Granisetron TDS is approved in several countries outside the EEA. The indication sought is prevention of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy for up to 5 consecutive days.

2.2. Quality aspects

2.2.1. Introduction

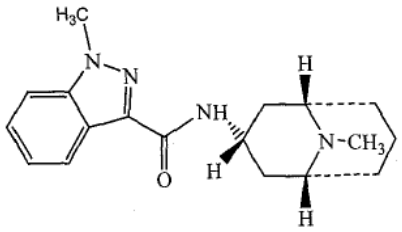
Granisetron TDS consists of an active matrix spread on to a polyethylene terephthalate backing. The active matrix has an area weight of 110 g/m^2 (572 mg per patch). The active matrix consists of a pressure sensitive adhesive containing 6 % (w/w) granisetron base. The total content of the active drug substance is 34.3 mg per patch and the flux determined during the clinical programme using patches made by the proposed commercial product manufacturer is 3.1 mg/24 h.

2.2.2. Active substance

At the time of the CHMP opinion, the active substance granisetron is not described in the European Pharmacopoeia.

Granisetron is an off-white to pale yellow coloured powder, non hygroscopic, freely soluble in methanol and methylene dichloride. A single crystalline form of granisetron is consistently produced; no further studies on polymorphism were performed.

The molecular formula of granisetron is $C_{18}H_{24}N_4O$, its relative molecular mass 312.41 and its structural formula as follows:



Manufacture

The active substance is sourced from two different manufacturers: Dr Reddy's Laboratories (Andhra Pradesh, India) and Cipla Ltd (Mumbai, India). Both sources of drug substance are supported by Active Substance Master Files.

Granisetron base manufactured by both drug substance suppliers is generally produced by the same manufacturing process as granisetron hydrochloride. The active substance from Cipla Ltd is manufactured to the point of granisetron base with manufacture halted before conversion to the hydrochloride salt, while the active substance from Dr Reddy's Ltd is manufactured to the point of granisetron hydrochloride and then converted to granisetron base. Applicant states that due to the above presented approaches, the impurity profile of both sources of granisetron base drug substance is, therefore, the same as for the respective granisetron hydrochloride salts manufactured by both Cipla Ltd and Dr Reddy's Ltd.

The synthetic routes are considered essentially identical except for a few minor details and would be expected to produce finished product of identical quality with very similar impurities profiles. The solvents used by the two processes have some differences, which are reflected in the residual solvents specifications for the respective active substances.

The active substance produced by Cipla Ltd. is dried, milled and sieved; the active substance produced by Dr Reddy's Laboratories Limited is dried and sieved. Since the granisetron base is dissolved in N,N-dimethylacetamide during the granisetron TDS manufacturing process, there is no particle size specification and the active substance physical characteristics have no influence on the quality of the drug product. The granisetron base produced by both Cipla Ltd. and Dr. Reddy's Laboratories Limited is the endo form. Thus the Applicant considers two granisetron base sources can be considered equivalent with respect to the manufacture of granisetron TDS.

The quality of the starting material supplied by different manufacturers is satisfactory. The manufacturing processes are well established and reproducible and the specification of granisetron ensures that the product fully meets the requirements. Adequate details are provided for the quality control testing performed during the synthesis; these include specifications and the associated test methods for all the raw materials used in the process plus any in-process testing also with limits and test method. These procedures and tests ensure that the processes are properly and adequately controlled. Batch analysis from production scale batches, are provided ensuring consistency in the manufacture of the active substance.

Specification

As the active substance in Sancuso preparation, presented in a form of granisetron base, is identical to the active moiety of the reference product Kytril 1 mg Tablet (granisetron hydrochloride), for the purposes of setting specifications the existing European Pharmacopoeia (Ph. Eur.) monograph for granisetron hydrochloride has been considered.

Specifications have been set that are appropriate in view of the Ph Eur Monograph 'Substances for Pharmaceutical use', ICH guidance.

The specifications of the active substance as tested by the finished product manufacturer include the following test parameters: description, solubility, identification (HPLC and IR), water content (LoD), residue on ignition, heavy metals, related substances (HPLC), assay (HPLC), particle size and residual solvents (GC).

Batch analysis results of at least 3 production scale batches from each manufacturer demonstrate compliance with the proposed specification and indicate that the manufacturing process followed by both manufacturers is under control.

Stability

Satisfactory stability data of three batches from each manufacturer of the active substance stored in their proposed commercial packaging at 25 °C/ 60 % RH or 30 °C/ 65 % RH and 40 °C/ 75 % RH, have been provided to support the proposed re-test period of 24 months. The following tests were included in the stability program: description, identification, loss on drying, related substances and assay. The container closure system is similar to that proposed for commercial packaging. All results comply with the specifications and no trends are observed.

2.2.3. Finished medicinal product

Pharmaceutical development

Granisetron TDS consists of a stable matrix of granisetron base (6% w/w: 34.3 mg/52 cm2 patch) in a commercially available adhesive (Duro-Tak 387-2287).

Granisetron base was selected as the active drug substance in preference to granisetron hydrochloride (the form of the drug used in currently marketed oral and intravenous formulations and described by a Ph. Eur. compendial monograph) because of anticipated superior skin permeation properties. Granisetron base is lipophilic, non-ionic drug substance and due to its physical/chemical properties it is more suitable for the preparation of transdermal dosage forms and for appropriate penetration through the skin.

The objective of the granisetron TDS formulation development programme was to create a stable granisetron transdermal matrix system capable of delivering the active substance over multiple days whilst achieving the necessary plasma levels. The pharmaceutical development process focused on the manufacturability and stability of the formulation, and permeation and loading of the active substance. The pharmaceutical development is presented in sufficient details and is supported by adequate amount of experimental data. Adequately designed and reported comprehensive validation studies are presented. Steps in formulations development and manufacturing process development are logical and consistent.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process involves several processing steps such as manufacture of the adhesive blend containing Granisetron base, spreading of the blend onto the siliconised liner, followed by drying,

rolling the backing onto the dried adhesive matrix and finalising by punching and packaging the patches. The description of manufacturing process and process controls is presented in sufficient detail and process flow diagram is presented with indication of the critical steps, including appearance, identification of granisetron, assay, and residual solvents. The manufacturing steps are conducted for a 40 kg batch size.

Process validation results of four production scale batches were provided. Results of tested parameters are batch to batch comparable and are within proposed limits. The results verify that the process assures adequate batch to batch consistency.

Product specification

The specification of the drug product are acceptable and include: appearance, assay (HPLC), uniformity of dosage units, identification by HPLC and UV, related substances (HPLC), presence of crystals, dissolution, microbiological purity, pouch integrity, adhesion and peel force. The finished product specifications are adequate for controlling this pharmaceutical form. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur. and ICH guidelines. All tests included in the specification have been satisfactorily described and validated.

Certificates of analysis of seven production scale batches are provided. The batch analysis results show that the finished product meets the proposed specifications and confirm the consistency & uniformity of manufacture indicating that the process is under control.

Stability of the product

The conditions used in the stability studies are in accordance with the ICH stability guideline (25 °C/ 60 % RH, 30 °C/ 65 % RH and 40 °C/ 75 % RH) and the packaging similar to that proposed for the market. The control tests and specifications of drug product are adequately drawn up. Photostability tests performed on one batches showed that the product is unstable at when exposed to UV and cool white light but that the proposed container closure system adequately protected the product from light. Based on the stability data provided the proposed shelf-life of 3 years when stored in the original packaging at 25 °C with allowable excursions to 30 °C can be granted.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature as well as studies conducted by the applicant to support this application. In accordance with the requirements for a hybrid application, the applicant has identified a programme to address the following points:

(1) whether administration of granisetron base via the transdermal route results in a comparable systemic toxicological profile to that established following oral and intravenous administration of granisetron hydrochloride, and

(2) whether transdermal administration of granisetron base exhibits the potential for local irritation or photosensitivity.

The safety programme undertaken by the Applicant comprises the following studies:

- 14-day local tolerance and systemic toxicity studies in rat and dog, which compared the effects of granisetron administration via different routes: transdermal versus oral versus intravenous (i.v). bolus injection
- 14-day toxicology studies via continuous i.v. infusion in rats and dogs in order to further increase systemic exposures to granisetron (rat) and maintain plasma granisetron concentrations constant over the whole duration of the treatment period (rat and dog)
- Six additional, non-pivotal repeat-dose toxicity studies
- Skin sensitising potential in the guinea-pig according to the Buehler protocol
- *In vitro* photosafety studies in Balb/c 3T3 fibrobasts and Chinese hamster ovary cells
- *In vivo* photoirritation and photosensitisation study in guinea-pigs.

Furthermore, an environmental risk assessment was performed.

All pivotal non-clinical studies provided with this application were performed according to the GLP standards.

2.3.2. Pharmacology

Granisetron was previously demonstrated to be potent and effective in the anaesthetised rat, cat and in the conscious ferret with a long duration of action and a shallow dose/inhibition curve. Relatively large changes in granisetron levels are required to result in marked changes in anti-emetic effect. Noteworthy findings during preclinical general pharmacological testing with granisetron were observed at very high doses in vivo and very high concentrations in vitro, and were considered unlikely to be clinically relevant. Later findings of possible inhibition of the human cardiac ion channels was taken into account in clinical studies with granisetron TDS (Study 392MD/39/C).

2.3.3. Pharmacokinetics

The absorption patterns following IV administration of 14C-granisetron to rats and dogs suggest no differences in Cmax, t1/2, and AUC of granisetron between the single-dose and repeated-dose groups (Haddock, 1990[1]). There is no indication in the literature of a gender difference in PK in animals.

[1] Haddock, R.E., 1990. Pharmacokinetics of granisetron hydrochloride - Distribution,

Elimination of IV granisetron was both urinary (40 %) and faecal (60 %) in both rats and dogs and it is unlikely that granisetron undergoes significant enterohepatic circulation.

2.3.4. Toxicology

Single dose toxicity

Median lethal dose values for the rat and mouse are described by Hakansson et al., 1990[1]. The acute toxicity of granisetron was primarily due to CNS stimulation with convulsions occurring in rats and mice after oral, subcutaneous and IV administration.

Repeat dose toxicity

The pivotal programme consists of two 14-day local tolerance and systemic toxicity studies in rats and dogs, comparing granisetron administration via the TDS route versus the oral and IV (bolus) routes, as well as two 14-day continuous IV infusion toxicology studies were performed in rats and dogs. In total, the applicant has performed 8 repeat-dose toxicity studies. These studies are summarized in the table below.

Study ID	Species/ Sex/ Number/Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
19137/05 (Non pivotal studies) GLP – Yes	Rat (CD/Crl: CD (SD))/ M3/group	Patch (with 6 % granisetron base) sizes (% BSA): 2 %; 5 %;10 % Transdermal	7 day		Well-defined erythema in 2 of 3 animals and very slight erythema in 1 of 3 animals in the 10% group. 1 of 3 animals revealed well-defined erythema and 2 of 3 animals very slight erythema in the 5% and 2.5% groups, respectively. No changes in: behaviour; external appearance; faeces; body weight; body weight gain. No treatment-related pathological findings or premature deaths.
19292/05 (Non pivotal studies) GLP – Yes	Rat (CD/Crl: CD (SD))/ M3/group	1; 3; 9 mg/kg/day/ Continuous IV infusion (granisetron HCl in saline)	7 day		No clinical signs of systemic toxicity. No treatment-related changes in: faeces; body weight; food or drinking water consumption. No treatment-related macroscopic post mortem findings or premature deaths.
19139/05 (Non pivotal studies) GLP – Yes	Dog (Beagle)/ M3	Patch (with 6 % granisetron base) sizes (% BSA): 5 % followed by 10 %; Transdermal	7 day for each patch size		Very slight local erythema. No signs of systemic intolerance. No treatment-related changes in: faeces; body weight; food or drinking water consumption. No premature deaths.

metabolism, and elimination following intravenous administration to rats and dogs, The Clinical Report, 24, p.6821

[1] Hakanson S, et al, 1990; Toxicilogical study of granisetron hydrochloride; The Clinical Report 24, p. 4991

Study ID	Species/ Sex/ Number/Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
19335/05 (Non pivotal studies) GLP – Yes	Dog (Beagle)/ M1/group	0,3; 1; 3; mg/kg/day/ Continuous IV infusion (granisetron HCl in saline)	7 day		No clinical signs of systemic toxicity. No treatment-related changes in: behaviour; faeces; body weight; food or drinking water consumption. No treatment-related local intolerance at infusion site or premature deaths.
19138/05 (Pivotal studies) GLP – Yes	Rat (CD/Crl: CD (SD))/ M10/F10/group	Patch (6 % granisetron base): 10 % BSA; Transdermal. 50 mg/kg/day; p.o. 0; 1; 9 mg/kg/day; IV	14 day	Transdermal (6 % granisetron base): 10 % BSA; p.o. (granisetron HCl): 50 mg/kg/day IV (granisetron HCl): 1 mg/kg/day	Transdermal: Local intolerance reactions in the form of a moderate or severe erythema were noted at the application sites of the animals treated epicutaneously. The local reactions observed are considered to be due to the adhesive 14-day patch application causing a local irritation of the skin. No signs of systemic toxicity. Oral administration: No signs of systemic toxicity. Intravenous administration: No signs of local and systemic toxicity were noted for the animals treated intravenously with 1 mg /kg/ b.w./day. 9 mg /kg/ b.w./day IV caused tonicoclonic convulsions in a few male and female animals on individual test days, lasting for up to 5 minutes after the injection. Histopathological examination revealed an increased incidence and severity of granulation tissue with haemorrhage at the intravenous injection sites.
19293/05 (Pivotal studies) GLP – Yes	Rat (CD/Crl: CD (SD))/ M10/F10/group	0; 1; 3; 9 mg/kg/day/ Continuous IV infusion	14 day	9 mg/kg/day	No mortality. No clinical signs of toxicity were noted at any dose level. No effect on the body weight and the food consumption. No test item-related influence was observed on haematological, biochemical and urinary parameters. No effect on the eyes and the auditory acuity at any dose level. Macroscopic *past martern* evaluation revealed no systemic changes during necropsy considered as related to the treatment with the test item. The absolute and relative organ weights were in the normal range. The bone marrow examination revealed no test item-related findings. The histopathological evaluation revealed no test item-related local or systemic microscopic findings.
19140/05 (Pivotal	Dog (Beagle)/ M3/F3/group	Patch (6 % granisetron	14 day	Transdermal (6 %	Transdermal: No test item-related signs of local toxicity

Study ID	Species/ Sex/ Number/Group	Dose (mg/kg b.w.)/ Route/	Duration	NOAEL (mg/kg/ day)	Major findings
studies) GLP – Yes		base): 10 % BSA; Transdermal. 2 mg/kg/day; p.o. 0; 0,3; 3 mg/kg/day; IV		granisetron base): 10 % BSA; p.o. (granisetron HCl): 2 mg/kg/day IV (granisetron HCl): 0,3 mg/kg/day	were noted for the animals treated epicutaneously with a Granisetron 6% Laminate patch. No signs of systemic toxicity. Oral administration: No signs of systemic toxicity. Intravenous administration: No signs of local and systemic toxicity were noted for the animals treated intravenously with 0.3 mg Granisetron HCl/kg b.w./day. 3 mg Granisetron HCl/kg b.w./day IV caused salivation in one male and two female animals on one test day, lasting for up to 20 minutes after the injection.
19336/05 (Pivotal studies) GLP – Yes	Dog (Beagle)/ M3/F3/group	0; 0,3; 1; 3 mg/kg/day; IV (continuous infusion)	14 day	3 mg/kg/day	No mortality. No clinical signs of toxicity were noted at any dose level. No influence on the body weight and the food consumption. No influence on haematological and biochemical parameters, circulatory functions, the ECG-parameters, urinary status and during the ophthalmological and auditory examinations at any of the dose levels. Macroscopic *post martern* evaluation revealed no systemic changes during necropsy that are considered to be related to the treatment with the test item. The absolute and relative organ weights were in the normal range. The bone marrow examination revealed no test item-related findings. The histopathological evaluation revealed no test item-related local or systemic rnicroscopic findings.

No new signals were identified by the Applicant with the exception of local intolerance in the form of erythema at the application sites. The formulation of the granisetron TDS used in the toxicology studies was the same formulation composition, containing the same strength as that used in the clinical trials and the same as the proposed commercial composition.

Genotoxicity

The genotoxicity of granisetron has been studied by the originator with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations in vitro. No significant genotoxic effects could be observed.

Carcinogenicity

Carcinogenicity studies conducted by the originator showed no special hazard for humans when used at the recommended dose. In accordance with the recommendations of ICH S1A (treatment duration

below 6 months and patient population) no new genotoxicity studies have been performed for granisetron TDS.

Reproduction Toxicity

Reproductive and developmental toxicity was previously studied with po and sc fertility studies in rats, po and iv embryofetal development studies in rats and rabbits (only po), po and sc pre and post-natal development studies in rats. These studies demonstrated no effects on fertility, no embryotoxicity or effects on development and reproductive performance of pups, at maximum doses which were sufficiently high to produce parental toxicity.

Toxicokinetic data

Toxicokinetic analysis was performed from the repeat dose toxicity studies in rats and dogs. The results are summarized in the following table.

Results of toxicokinetic analysis in rats and dogs using administration of granisetron

	AUC(ng·h/ml)			
	Rats		**Dogs**	
	M	**F**	**M**	**F**
Transdermal				
Patch: 2,5% BSA[#]	AUC_{0-144h} : 376	-	-	-
Patch: 10% BSA[#]	AUC_{0-144h} : 491	-	AUC_{0-168h} : 2404	-
Patch: 10% BSA	AUC_{0-144h} : 1394		AUC_{0-168h} : 2285	
Patch: 10% BSA (14 day study)	Mean daily AUC: 219	Mean daily AUC: 440	Mean daily AUC: 1100	Mean daily AUC: 665
Oral				
2 mg/kg p.o. capsules			AUC_{0-8h}: 243[*]	AUC_{0-8h}: 139[*]
50 mg/kg p.o. gavage	AUC_{0-4h}:1793[*]	AUC_{0-4h}: 1675[*]	-	-
Intravenous				
0,3 mg/kg			AUC_{0-8h}: 75[a] Mean daily AUC: 74[b]	$AUC_{0-8h:}$ 62[a] Mean daily AUC: 75[b]
1 mg/kg	AUC_{0-5h}: 111[a] Mean daily AUC: 164[b]	AUC_{0-5h}: 100[a] Mean daily AUC: 140[b]	Mean daily AUC: 237[b]	Mean daily AUC: 185[b]
3 mg/kg	Mean daily AUC: 502[b]	Mean daily AUC: 386[b]	AUC_{0-8h}: 812[a] Mean daily AUC: 755[b]	AUC_{0-8h}: 626[a] Mean daily AUC: 579[b]
9 mg/kg	AUC_{0-5h}: 1019[a] 1618[b]	AUC_{0-5h}: 856[a] 1086[b]		

[1] Preliminary 7 day study; * after 7th administration (14 day study); [a] IV bolus; after 7th administration (14 day study); [b] continuous 24 hour IV infusion (14 day study)

Local Tolerance

The local tolerance of granisetron TDS was investigated in the repeat-dose toxicity studies performed by the Applicant in rats and dogs which revealed a low potential for irritancy for granisetron TDS.

In addition, the applicant has conducted a specific local tolerance and sensitisation study in guinea-pigs No sensitising properties were observed in this study

Other toxicity studies

Phototoxicity

The Applicant conducted 2 in vitro studies and 1 in vivo study in female guinea-pigs (Report 21022/06) to assess the phototoxic potential of granisetron base as well as an in vivo photosensitisation test in guinea-pigs (see table below). The phototoxicity studies are not showing any phototoxicity, photoirritation, or photosensitisation potential. However the results of a single in vitro study in CHO cells suggest that there is a potential for photoactivation of granisetron as this is shown in a dose-dependent and statistically significant increase in chromosome structural damage following photoirradiation. This finding is reflected in sections 4.4. and 5.3 of the SmPC.

Summary of phototoxicity studies with granisetron

Study type/ Study ID/ GLP	Species/Strain	Route (Vehicle/ Formulation)	Duration of Dosing	Doses	Major findings
2776/1 GLP- Yes	Mouse Balb/c 3T3 fibroblasts	In vitro solution in culture medium	1 hour pre-irradiation + 83 minutes with or without irradiation with UV-A (5 J/cm2).	0.32-1000 µg/mL Grani-setron base	IC50 in non-irradiated cells: 864.8 µg/mL. IC50 in irradiated cells: 519.6 µg/mL. The photoirritation factor (IC50 without irradiation/ IC50 with irradiation) is <2 indicating that granisetron base is non-phototoxic.
2776/2 GLP- Yes	CHO cells	In vitro solution in culture medium	2-3 hours (15 min preincubation + ≥2 hours postirradiation with UV-A:UV-B light).	50-380 µg/mL	In irradiated cells, a dose-dependent and statistically significant increase in chromosome structural damage at 200 and 300 µg/mL (13 and 33 % cells, respectively compared to 2.5 % in irradiated vehicle control cells).
21022/06 GLP- Yes	Guinea pigs	Transdermal	Application of patches for 3 or 4 day periods with irradiation after each wear period. Challenge application for 3 days, 11 days after last irradiation	Single Grani-setron TDS	No indication of irritancy (non-irradiated animals) or of photosensitisation

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has conducted an experimental determination of the octanol-water partition coefficient (Kow) of granisetron, using the shake-flask method. A log Kow value of 2.84 ± 0.25 (n=6) was calculated, which is close to the computed value of 2.8, previously submitted, and is below the log Kow limit value of >4.5. Therefore the substance is not a PBT.

For calculating PECsw both (1) the total amount of granisetron within the granisetron TDS, whether this enters the environment through use or after removal of the patch, and (2) the amount released during actual use have been considered by the applicant.

Only the first approach is being used by CHMP as basis for the calculation, as the active substance remaining in the patch discarded after use can have also an impact on the environment and because this is the most conservative approach.

According to the Q&A CHMP Guideline on the ERA of medicinal products for human use (EMA/CHMP/SWP/44609/2010), note 1, Fpen can be refined taking into account the prevalence data provided and the treatment regime.The incidence of all new cancers is estimated in EU at 3.2 million and the prevalence of all cancers (based on Globocan 2008) at 3.4 million.

In the worst case scenario, granisetron TDS is given as 7 patches/week in 12 courses of chemotherapy in a 12 month period. Considering that each patch contains 34.3 mg of granisetron, and taking into account the dosing regime, calculated (average) Doseai = 34.2 mg *7 *12/365 = 7.9 mg.

Taking the prevalence as 3.2 million (out of 498 million inhabitants in EU), the refined Fpen is 3.2/498= 0.0064.Therefore the calculated PECsw= (7.9*0.0064)/(200*10)= 0.025 10-3 mg/L= 0.025 μg/L, which is above the action limit of 0.01 μg/L.

Consequently, the applicant was asked to perform a phase II ERA. The applicant should perform a phase II ERA based on literature with a view to propose amendments for the information for use and handling (& disposal) of the patches. Overall, considering that the actual use of granisetron TDS is likely to be far less than the above assumptions, it is considered reasonable in these circumstances to conclude at present that the therapeutic use of granisetron TDS is unlikely to pose a risk to the environment. Recommendations for disposal are included in the product information.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

The MAH is recommended to perform a literature based phase II ERA analysis, with a view to propose amendments for the information for use and handling (& disposal) of the patches.

2.3.6. Discussion on non-clinical aspects

The pharmacological properties of granisetron in the Non-clinical part are adequately overviewed on the basis of scientific publications. The Applicant has not conducted any new pharmacokinetic nonclinical studies and nowadays available data are discussed and reviewed in the Nonclinical Overview part. Data on the toxicology of granisetron TDS are based on bibliographical sources on granisetron and repeat-dose toxicity, local tolerance, photogenotoxicity and photosensitisation studies conducted by the Applicant according to the GLP standards.

In the repeat dose toxicity and the toxicokinetic analysis no new signals were identified with the exception of local intolerance in the form of erythema at the application sites. The formulation of the Granisetron TDS used in the toxicology studies was the same formulation composition, containing the same strength as that used in the clinical trials and the same as the proposed commercial composition.

In addition, the Applicant has conducted a specific local tolerance and sensitisation study in guinea-pigs. Different grades of skin irritations were observed in granisetron base-treated animals, as well as erythema in all positive controls.

Application site erythema and application site irritation were added to the RMP as important potential risks furthermore application site reaction was reflected in 4.4 of the SmPC.

The Applicant has conducted 3 formal studies to assess the phototoxic potential of granisetron base as well as an in vivo photosensitisation test in guinea-pigs. The phototoxicity studies are not showing any phototoxicity, photoirritation, or photosensitisation potential. However the results of a single in vitro study in CHO cells suggest that there is a potential for photoactivation of granisetron as this is shown

in a dose-dependent and statistically significant increase in chromosome structural damage. This finding is reflected in 4.4 and 5.3 of the SmPC.

With respect to the environmental risk assessment, it is considered reasonable to conclude at present that the therapeutic use of granisetron TDS is unlikely to pose a risk to the environment. Adequate recommendations for disposal are included in the product information. Nevertheless, a phase II ERA should be performed by the applicant with a view to propose amendments for the information for use and handling (& disposal) of the patches.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical program performed by the applicant was considered adequate to support this hybrid application. Issues observed in the performed studies such as application site erythema and photogenotoxicity were adequately addressed in the relevant parts of RMP and SmPC.

In the context of the obligation of the MAH to take due account of technical and scientific progress the MAH was recommended to perform a literature based phase II ERA analysis, with a view to propose amendments for the information for use and handling (& disposal) of the patches.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development strategies were designed to bridge to the previous findings of efficacy and safety for the reference product, the oral formulation of granisetron, to the transdermal formulation. Overall the study programme consisted of

- One pivotal phase III study in cancer patients
- One dose-ranging phase II study in cancer patients
- Nine pharmacokinetic studies
- One phase I pharmacology study.

The below table provides an overviews of this study programme.

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study Code Type of Study/Study Objectives	**Study Design and Type of Control**	**Patient Population**	**Number of Subjects**	***Dosage / Site and* Duration of Application**
Healthy volunteers				
392MD/4/C Phase I: Systemic bioavailability and tolerance of granisetron TDS in healthy subjects	Open-label, single center, single dose study	***Healthy male and*** female subjects	12 Enrolled 12 Treated (6 males and 6 females) 12 Completed	Granisetron TDS 15 cm² patch (9.9 mg) and placebo patch applied on the abdomen for 5 days
392MD/11/C Phase I: Comparative bioavailability study of 3 doses of granisetron	Open-label, randomized, single center, 4	Healthy male Subjects	12 Enrolled 12 Treated	Granisetron TDS: 15 cm² (9.9 mg), 33 cm² (21.8 mg) and 52 cm² (34.3 mg) patch

Study Code Type of Study/Study Objectives	Study Design and Type of Control	Patient Population	Number of Subjects	*Dosage / Site and* Duration of Application
TDS with daily dosing of oral granisetron in healthy subjects	treatment, 4 period, crossover study		*12 Completed*	applied on the upper arm for 6 days Oral group: Once daily dose of 2 mg granisetron tablet for 5 days
392MD/26/C Phase I: Skin sensitization and irritation potential of granisetron TDS Assesment of the delivery of granisetron from the patch by measuring plasma concentrations in a subset of subjects during the first 7-day patch application	Double-blind, randomized, single center, placebo controlled study	Healthy male and female subjects	212 Enrolled 212 Treated (54 males and 158 females) 202 Completed both phases Pharmacokinetics: 24 Enrolled and Treated (12 males, 12 females)	52 cm² patches (34.3 mg) and three placebo patches applied successively on the upper arm for 7 days each (total duration of exposure: 21 days) Challenge test: one 52 cm² patch (34.3 mg) and one placebo patch applied on the back for 2 days
392MD/39/C Phase I: Evaluate the placebo-corrected change from baseline in QTc. Evaluate ECG parameters, relationship between QTcF baseline change and plasma granisetron, patch adhesion and residual dose.	Single-blind, randomised, placebo controlled, single centre study.	Healthy male and female subjects	240 Randomised 240 Treated 239 Completed	Granisetron TDS 52 cm² patches (34.3 mg) applied to upper arm for 6 days or matching placebo (Treatment D: 4 day application only) Granisetron IV: 10 mcg/kg over 30 seconds or "matching" placebo Moxifloxacin hydrochloride (Avelox): 400 mg tablet
392MD/40/C Phase I: Assess the PK profile, safety and patch adhesion in elderly, underweight and obese subjects. Compare the PK profile of the patch obtained in elderly subjects with that obtained in younger subjects and in underweight and obese subjects with that obtained from subjects with normal BMI.	Single-centre, open label, single-dose, two-part, controlled study	Healthy male and female subjects	60 Enrolled 60 Treated 59 Completed	One 52 cm² (34.3 mg) granisetron TDS applied upper arm on Day 1 for 7 days.
392MD/41/C Phase I: Assess the safety and PK profile of the co administration of IV granisetron and Granisetron TDS Assess patch adhesion and residual granisetron after	Open-label, single arm, single-centre study	Healthy male and female Caucasian subjects	12 Enrolled 12 Treated 12 Completed	One 52 cm² (34.3 mg) granisetron TDS applied to upper arm on Day 1 for 7 days, second patch applied on Day 8 for 7 days. IV granisetron 0.01 mg/kg (maximum 1

Study Code Type of Study/Study Objectives	Study Design and Type of Control	Patient Population	Number of Subjects	*Dosage / Site and* Duration of Application
patch use.				mg) on Day 1
392MD/43/C Phase I: Assess the effect of locally applied heat on the PK profile of granisetron delivered from granisetron TDS Assess safety and tolerability, residual granisetron after granisetron TDS use and calculation of in vitro flux.	Single-centre, open label, randomised crossover study.	Healthy male and female subjects	16 Enrolled 16 Treated 16 Completed	One 52 cm² (34.3 mg) granisetron TDS to upper arm for 5 days, and a second Granisetron TDS applied for 5 days after minimum washout of 14 days. Cura-Heat® Back & Shoulder pad applied over the granisetron TDS patch on each of the 5 days for 4.5 continuous hrs.
SP-0101 Phase I: Assess safety and tolerability and PK of granisetron TDS after a single 6-day application in healthy male Japanese subjects.	Randomised, double blind, Placebo controlled, single centre study	Healthy male Japanese subjects	12 Enrolled 12 Treated 12 Completed	Granisetron TDS 52 cm² (34.3 mg) or placebo applied to upper outer arm for 6 days.
Cancer patients				
392MD/8/C Phase II: Compare the efficacy, safety and tolerability of granisetron TDS with oral granisetron in Chemotherapy Induced Nausea and Vomiting (CINV) following a single day administration of moderately emetogenic chemotherapy	Double-blind, double dummy, randomized, multicenter, parallel group study	Male and female patients with histologically and/or cytologically confirmed solid tumours with ECOG of ≤ 2 receiving single day moderately emetogenic chemo-therapy	179 Randomized 173 Treated (63 males and 110 females) Granisetron TDS group 88, oral granisetron group 85	Granisetron TDS group: 52 cm² patch (34.3 mg) applied on the upper arm for 5 days in combination with oral placebo Oral group: One capsule containing two 1 mg tablets in combination with a placebo patch
392MD/15/C Phase III: Compare the efficacy, safety and tolerability of granisetron TDS with oral granisetron in Chemotherapy-Induced Nausea and Vomiting (CINV) following administration of moderately and highly emetogenic multi-day chemotherapy	Double-blind, double dummy, randomized, multicenter, parallel group study	Male and female patients with CINV associated with the administration of moderately or highly emetogenic multi-day chemotherapy	641 Randomized 637 Treated (314 males and 323 females) 621 Completed	Granisetron TDS group: 52 cm² patch (34.3 mg) applied on the upper arm for 7 days in combination with oral placebo Oral group: One capsule containing two 1 mg granisetron tablets/day for up to 5 days (on day of chemotherapy) in combination with a placebo patch

2.4.2. Pharmacokinetics

The pharmacokinetics of granisetron TDS have been studied in all ten clinical studies involving 1,386 subjects (576 healthy subjects and 810 cancer patients with CINV), of whom approximately 58 % were the target patient population - cancer patients undergoing chemotherapy. The release of granisetron from granisetron TDS was measured in nine of these. No formal study has been performed to assess granisetron TDS pharmacokinetics in children.The measurement was made by determining the residual amount of granisetron that remained in the granisetron TDS after removal and calculating the administered dose as patch content minus residual granisetron amount. The in vitro flux, that is the dose released per day (apparent dose), could then be calculated as released dose/days contact.

The in vitro flux has been dose normalised, for comparison purposes, to a dose of 34.3 mg, that is, to a 52 cm2 patch. Adjusting the total apparent dose (21.7 mg) from this study for number of days' exposure (7 days) yields a flux value of 3.1 mg/24 h. Thus, the granisetron TDS flux has been calculated as 3.1 mg/24 h.

Bioanalytical methods

Bioanalytical methods for granisetron were adequately described and validated to support the clinical pharmacokinetic programme conducted. The analytical methods used in each study are listed in Table 2.

Table 2: Overview of Bioanalytical Methods

Method	**Bioanalytical Laboratory**	**Validation Report /Method Number**	**Study Number**
HPLC with fluorescence detection	Nuvisan Pharma Services GmbH & Co. KG (formerly AAI, Neu-Ulm, Germany)	AAI study code NX012 MOP-NX012 version D01	392MD/4/C 392MD/11/C 392MD/8/C 392MD/15/C 392MD/26/C
LC MS/MS assay	Nuvisan Pharma Services GmbH & Co. KG (formerly AAI, Neu-Ulm, Germany)	AAI study code TX008 MOP_TX008 version D01	392MD/39/C 392MD/40/C 392MD/41/C 392MD/43/C SP-0101

Absorption

Study 392MD/4/C. This was a single-centre, single-dose, open, Phase I study and was conducted in 12 healthy subjects (6 males and 6 females) to evaluate the systemic bioavailability of one 15 cm² granisetron TDS and to determine the PK profile over an application period of 5 days on the abdomen. For the evaluation of the plasma concentrations of granisetron, blood samples were drawn per time point at the following times after patch application: 0 (pre-dose), 0.5, 1, 3, 6, 10, 14, 18, 24, 30, 36, 48, 60, 72, 84, 96, 108, 120 (preceding patch removal), 126, 132 h after patch application. Pharmacokinetic parameters were calculated by non-compartmental or model free methods, namely, linear trapezoidal rule for AUC, log-linear regression for λz. PK parameters are given in the table below.

Mean (CV %) Granisetron PK Parameters After Application of One Single 15 cm² Granisetron TDS Patch on the Abdomen For 5 Days to Healthy Subjects (n = 11) Study 392MD/4/C:

		t_{max} (h)[a]	$AUC_{(0-132h)}$ (ng/mL.h)	C_{avg} (ng/mL)	*In vivo* flux (mg/24h)[b]
All Subjects	1.86 (72)	48 [30-126]	148 (80)	1.12 (81)	1.47 (80)
Males (5)	2.26 (75)	48 [30-48]	185 (76)	1.43 (77)	2.06 (66)
Females (6)	1.53 (64)	48 [48-126]	117 (82)	0.89 (83)	0.98 (80)

a: median [min-max] b: *In vivo* flux= C_{avg}*CL with CL representing granisetron i.v. clearance of 0.79 L/h.kg (Allen et al. 1995)

This study was contributing to the first understanding of mean Tmax determination that was found as 48 hrs, and ranging form 30 to 126 hrs.

The CHMP noted that in this study were a number of outliers, with both higher and lower exposures within this study. The observed variability in PK parameters was in line with the known high variability for oral and IV granisetron.

Different application sites were used in study 392MD/4/C (abdominal wall) compared to the other clinical trials presented (upper arm). Data from this study show that somewhat higher concentrations are obtained in comparison with Study 392MD/11/C (patch applied on upper arm). Further, in the patient studies it was specified that in cases of breast cancer and lymph gland issues prevented use of the upper arm, the patch should be applied to the patient's upper abdomen. However, no subgroup analyses could be performed from these patient studies as only one patient applied the patch to another site. As no safety issues are expected from the observed higher concentrations, the CHMP accepted the companies proposal to use the abdomen as an alternative administration site if an arm is not available, which is reflected in the SPC Section 4.2.

Study 392MD/11/C. This was a single-centre, open-label, four-way-crossover study to compare the bioavailability of granisetron after a single 6-day application of three dosages of granisetron TDS, to that of once-daily dosing of 2 mg granisetron tablets for 5 days. This study also assessed the dose proportionality of granisetron pharmacokinetics after patch application.

Twelve healthy male subjects received oral granisetron administered as a 2 mg dose once daily, for 5 days and three dosages of granisetron TDS (15, 33 and 52 cm2) applied for 6 days to the upper outer arm. Each treatment was separated by a washout period of at least 5 days. The mean age of all 12 subjects was 37.1 years; mean weight 76.8 kg; and mean BMI (body mass index) 24.2 kg/m2.

Serial blood samples were taken before and up to 240 hrs after TDS application and up to 72 hrs after the last oral dose. The following pharmacokinetic parameters were calculated: Cmax, Tmax, t1/2,λz, AUC(0-z), AUC(0-∞), in vivo flux (for TDS only) and Cavg calculated as AUC(0-24h)ss/24 for oral dosing and as AUC(0-144h)/144 for TDS application. The apparent elimination half-lives (t1/2, λz) were calculated by non-compartmental analysis.

Descriptive statistics were calculated for plasma concentrations and pharmacokinetic parameters of granisetron.

As Tmax is a discrete variable, day effect was tested using a Kruskal-Wallis non-parametric test. Time for plasma concentrations of granisetron to reach steady state was assessed on Ln-transformed trough plasma concentrations (C24h) observed from days 1 to 5 using an analysis of variance with subject and day as main effects in the model followed by a Tukey's test. For TDS: Proportionality between the dose administered (size of the patch) and the pharmacokinetic parameters was assessed by means of an analysis of variance with subject, dose and period interaction as main effects in the model on the following Ln-transformed parameters: Cavg/dose, AUC(0-∞)/dose, in vivo flux/dose and t1/2,λz.

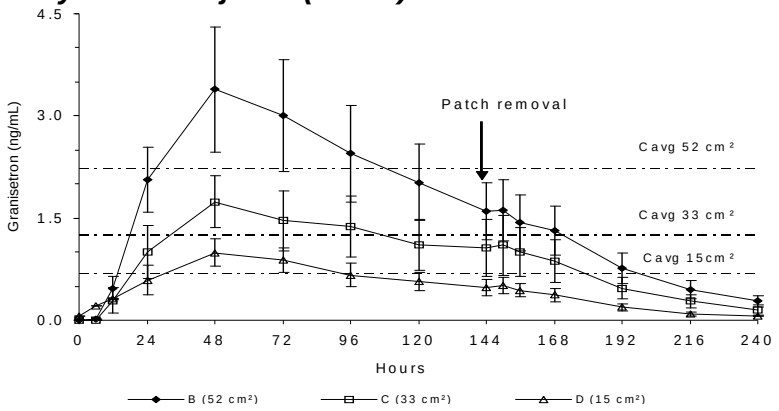
Mean granisetron concentration versus time curves for the three granisetron TDS administrations are presented in Figure 4 and the PK parameters are given in Table 4. This study was the basis for the decision to use the 52 cm2 for further clinical efficacy studies.

Table 4: Mean (CV%) PK Parameters After Application of Granisetron TDS for 6 Days to the Upper Arm of Healthy Subjects Study 392MD/11/C

Parameter	Unit	Granisetron TDS		
		15 cm^2	33 cm^2	52 cm^2
t_{max}[a]	h	48 [48-96]	48 [24-150]	48 [24-168]
C_{max}	ng/mL	1.15 (73)	2.08 (110)	3.85 (77)
C_{avg}	ng/mL	0.68 (83)	1.24 (110)	2.23 (89)
$AUC_{(0-\infty)}$	ng/mL.h	149 (70)[b]	287 (95)[c]	420 (89)
$t_{½}$	h	30.9 (32)[b]	30.9 (21)[c]	35.9 (35)
In vivo flux[d]	mg/24h	1.02 (86)	1.90 (110)	3.30 (93)
R_f		1.12 (48)	1.13 (70)	1.20 (69)

a: median [range] ; b: n=10 ; c: n=8 ; d: *In vivo* flux= C_{avg}*CL with CL representing granisetron i.v. clearance of 0.79 L/h.kg (Allen et al. 1995)

Figure 4: Mean (± SEM) Plasma Granisetron Concentration Versus Time After Application of One Granisetron TDS Patch (15, 33 and 52 cm^2) on the Upper Arm for 6 Days to Healthy Male Subjects (n=12)



Study 392MD/26/C. This study was a double-blind, placebo controlled study to assess the skin irritation and sensitisation potential of granisetron TDS and was undertaken in healthy subjects. The secondary objective was to assess the delivery of granisetron from the patch by determining the plasma granisetron levels in a subset of subjects. During the first 7-days administration of the patches a subset of 24 subjects had blood samples taken for plasma granisetron measurements to determine the release profile of the drug from the patch in the the to-be-marketed formulation.

The mean plasma granisetron Cmax and AUC values in healthy females were both approximately 3-fold higher than in males. Individual Cmax and AUClast values generally overlapped and part of the observed difference in mean values was caused by one female subject with Cmax and AUClast values 10-fold higher than those reported in other subjects (respectively, over 42 ng/mL and 4500 ng.h/mL). After this subject exclusion from the analyses, mean plasma granisetron Cmax and AUC values in healthy females were 1.8-fold higher than in males. Median Cmax and AUC values were 1.805 ng/mL and 169.05 ng.h/mL, respectively, in males and 4.92 ng/mL and 489.85 ng.h/mL, respectively, in females.

Study 392MD/39/C. This was a Phase I, single-site, single-blind (except for the use of moxifloxacin), randomized, placebo- and positive-controlled, 4-arm parallel study evaluating the effect of doses of

granisetron TDS (52 cm²) and i.v. granisetron on the QT interval in 120 healthy male and 120 healthy female subjects. The secondary objectives of this study were to assess the relationship between the QTcF change from baseline and plasma granisetron concentrations; and to assess patch adhesion and residual granisetron remaining in the patch after use. During the 5 day application of granisetron TDS, geometric mean Cmax and AUC_{0-120h} were 3.6 ng/mL and 239 ng.h/mL (see Table 5) respectively, with high intersubject variability (%CV 80% and 89%) respectively. Median time to maximum concentrations was 56 hours.

Table 5. Pharmacokinetic Results of Granisetron During 5-Day Application of Granisetron TDS

Pharmacokinetics of Granisetron	Granisetron TDS and i.v. Placebo (Treatment A)					
	All		Male		Female	
	Geometric Mean	%CV	Geometric Mean	%CV	Geometric Mean	%CV
N	59		30		29	
C_{max}, ng/mL	3.629	83.30	2.908	79.14	4.563	78.15
t_{max}, h	56.08 (23.82-119.83)		56.08 (23.83-119.83)		71.83 (23.82-119.83)	
AUC_{0-120h}, ng·h/mL	238.5	89.48	193.4	85.51	296.3	84.15

Study 392MD/40/C. This was a single-centre, open-label, single-dose, two-part, controlled study without randomisation, to assess the pharmacokinetic (PK) profile of the granisetron TDS in elderly subjects (part I) and to assess the PK profile of the granisetron TDS in underweight and obese subjects (Part II). Healthy male or female subjects; neither gender was to represent more than 60% of the population enrolled in each part of the study.

The results of the statistical analyses of the PK parameters Cmax, AUC(0−z), AUC(0−∞) and Cavg show that the there were no significant regression coefficients at the 5% level; therefore, the continuous variables age, BMI and age*BMI were determined to have no predicting properties for describing the PK parameters Cmax, AUC(0−z), AUC(0−∞) and Cavg.

Study 392MD/41/C. This was a Phase 1 study to assess the PK profile of the *co-administration* of i.v. granisetron and granisetron TDS (52 cm2) in 6 healthy male and 6 healthy female Caucasian subjects.

The times between 0 and 24 hrs at which peak plasma concentrations were reached (Tmax (0−<24)) ranged from 0.05 to 1 hour after i.v. administration of granisetron. Individual Tmax (24−168) and Tmax (>168−336) estimates ranged from approximately *24 to 96* hrs and from 192 to 264 hrs (i.e. 24 to 96 hrs after application of the second patch), respectively. Subsequent to these concentration maxima, plasma concentrations were variable but generally declined in a mono-exponential manner.

Based on geometric mean AUC(0−168) and AUC(168−336) estimates *no meaningful difference* in systemic exposure to granisetron was noted between the two granisetron TDS applications following co-administration of transdermal and i.v. granisetron.

The subsequent concentration maximally attributable to the release of granisetron from the granisetron TDS applied at 0 hour and 168 hrs were broadly comparable, in terms of their respective Cmax and Tmax values, and as such did not appear to be affected by i.v. co-administration.

Systemic exposure to granisetron was comparable following the first and second transdermal patch applications: minimal differences were apparent between Cmax(24−168) and Cmax(>168−336), and

between corresponding Cavg estimates, with minimal evidence of accumulation following *repeat dosing*.

The PK analysis from the Study (41/C) revealed that T max variations can be quite variable, ranging from 24 hrs up to 96 hrs. The applicant provided analysis of mean and median C24/Cmax values for 24 hours, 48 hours and 96 hours and stated that these concentrations were similar.

Study **392MD/43/C**. This was a Phase 1 study to evaluate the effect of external heat on the pharmacokinetics of granisetron TDS in 8 healthy male and 8 healthy female subjects. One granisetron TDS (52 cm2) was applied to the upper arm for 5 days (120 h), and a second granisetron TDS was applied for 5 days after a minimum washout of 14 days. On each of the 5 days (during either the first or second application), one Cura-Heat® Back & Shoulder pad with a measured local temperature of approximately 42ºC (107.6ºF) was applied over granisetron TDS at the same time each day and left in place for 4.5 continuous hrs. Subjects were randomised to receive Treatment A (granisetron TDS alone) followed by Treatment B (granisetron TDS plus Cura-Heat), or vice versa.Systemic exposure based on geometric mean estimates of Cmax, AUC(0−z), Cavg and AUC(0−∞) was comparable between the two treatments.

Time to maximum plasma granisetron concentration (Tmax) was also comparable between the treatments.

Apparent terminal half-lives were very similar between the treatments: mean apparent t½ estimates were 25.16 hrs for Treatment A (range 16.46 to 30.01) and 30.73 h for Treatment B (range 19.98 to 54.92).

Study SP-0101. This study was a Phase 1, single centre, randomized, double-blind, placebo-controlled study to assess the PK of a single 6-day application of granisetron TDS (52 cm2) in healthy Japanese males.

Following the application of a single 6-day granisetron TDS 52 cm2 to healthy male Japanese subjects, a median Tmax value of 48.0 hrs, as well as a mean t1/2 value of 30.7 hrs was observed for granisetron. Granisetron mean Cmax values of 5.02 ng/mL were also observed. Following granisetron TDS application, granisetron mean Cavg(0-144h) and Cavg(24-144h) were 3.00 ng/mL and 3.27 ng/mL, respectively. A similar moderate to large inter-subject variability was also observed in healthy male non-Japanese subjects in the 392/MD/11/C study.

Study 392MD/8/C. This was a multicentre, double-blind, double-dummy, randomised, parallel group, Phase 2 study in chemotherapy naïve patients undergoing a single day regimen of chemotherapy with MEC. A total of 175 patients received study medication and 157 were included in the per protocol (PP) population. The study included male or female patients 18-75 years of age with histologically and/or cytologically confirmed solid tumours, ECOG status ≥ 2 and a body mass index (BMI) of 18-30 kg/m2, who were scheduled to receive single-day administration of moderately emetogenic chemotherapy.

Blood samples for determining plasma levels of granisetron were taken 2 hrs following administration of the oral granisetron/placebo on Day 0 and thereafter on Days 1 and 4. In a small subset of 17 patients, samples were also taken on Days 5 and 6 after oral granisetron/placebo administration in order to establish the apparent terminal decline following removal of the patch on Day 4. Plasma concentration data were available for 86 patients on Day 0 granisetron TDS application (52 cm2 patch) and for 82 patients who had received a single 2 mg dose of oral granisetron.

In patients treated with a single 2 mg dose of oral granisetron absorption was rapid with granisetron quantifiable in the plasma of 80 out of the 83 patients one hour after chemotherapy. This time point was also Tmax and a mean plasma granisetron value of 7.17 ng/mL (median 7.01 ng/mL) was observed. In comparison, granisetron was similarly quantifiable in the plasma of 80 out of 86 patients

one hour after chemotherapy in patients receiving granisetron TDS. The mean value at this time point was 2.84 ng/mL (median: 1.12 ng/mL) and Cmax was not reached until 24 hours after chemotherapy (mean Cmax 5.00 ng/mL, median: 2.56 ng/mL).

For patients receiving oral granisetron the initial high Cmax was followed by a rapid decrease in plasma granisetron to 2.28 ng/mL 24 hours post dose and after 4 days plasma granisetron was below the limit of quantification in 70% of patients. Plasma granisetron levels decreased more slowly following granisetron TDS with plasma levels still as high as 3.26 ng/mL after 4 days. Two days after removal of granisetron TDS granisetron was still measurable in plasma, although it had decreased to 0.49 ng/mL. However, in oral granisetron patients no granisetron was quantified in plasma at this time point.

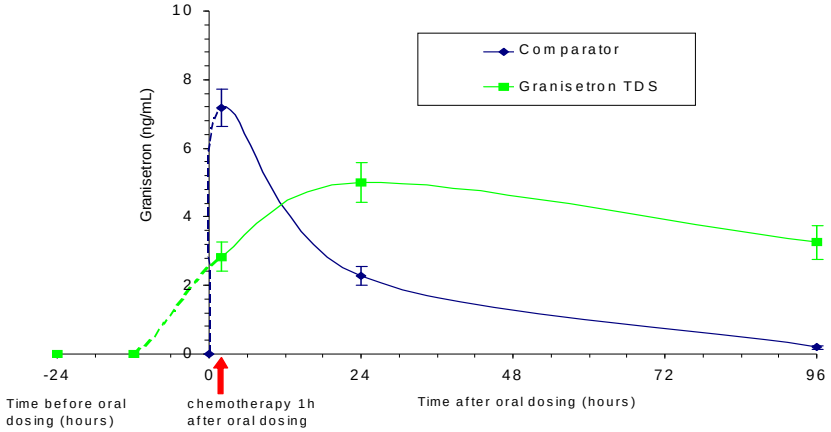
Table 12: Plasma Granisetron Concentrations (ng/mL) Following Granisetron TDS and Oral Administration in Study 8/C

Parameter	Time point				
	Day 0	Day 1	Day 4	Day 5	Day 6
Granisetron TDS					
N	86	85	79	10	10
Mean ± SD	2.84 ± 3.86	5.00 ± 5.32	3.26 ± 4.35	0.98 ± 0.87	0.49 ± 0.47
Min	<LOQ	<LOQ	<LOQ	0.22	<LOQ
Median	1.12	2.56	1.76	0.75	0.37
Max	17.20	28.10	27.40	2.63	1.50
CV	136.0%	106.4%	133.4%	88.7%	96.6%
Oral granisetron					
N	82	81	80	7	7
Mean ± SD	7.17 ± 4.90	2.28 ± 2.38	0.19 ± 0.44	0.04 ± 0.07	<LOQ
Min	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Median	7.01	1.62	<LOQ	<LOQ	<LOQ
Max	26.00	10.20	2.78	0.18	<LOQ
CV	68.3%	104.2%	229.8%	178.4%	-

<LOQ=below the limit of quantification (0.1 ng/mL)

The data are summarised in Table 12 and illustrated graphically in Figure 6.

Figure 6: Mean (± SEM) Plasma Granisetron Concentrations Following Granisetron TDS and Oral – (Comparator) Administration in Study 392MD/8/C



Study 392MD/15/C was a randomised, active control, double-blind, double-dummy, parallel-group, multi-national study to assess the efficacy, tolerability and safety of granisetron TDS (52 cm2 patch) in chemotherapy-induced nausea and vomiting (CINV) associated with the administration of moderately or highly emetogenic multi-day chemotherapy. Over six hundred patients were treated with granisetron (316 with the granisetron TDS and 321 with oral granisetron). Descriptive pharmacokinetic analyses were performed. Granisetron plasma concentration data are summarised for the two treatment groups, subdivided by sex, for Visit 1 and Visit 6 in Table 13.

Table 13: Plasma Granisetron Concentrations (ng/mL) Data from Study 392MD/15/C Subdivided by Treatment, Patients' Sex and Visit

Parameter	Time Point			
	Male Visit 1	Male Visit 6	Female Visit 1	Female Visit 6
Granisetron TDS				
N	102	104	128	126
Mean ± SD	4.06 ± 4.42	3.15 ± 4.25	3.74 ± 6.87	3.44 ± 4.44
Min	<LOQ	<LOQ	<LOQ	<LOQ
Median	2.89	1.57	1.41	2.12
Max	23.0	32.50	44.1	33.2
CV	108.8%	134.9%	183.8%	128.8%
Oral granisetron				
N	103	106	132	129
Mean ± SD	6.67 ± 6.26	0.88 ± 1.95	10.83 ± 9.95	1.07 ± 2.11
Min	<LOQ	<LOQ	<LOQ	<LOQ
Median	5.18	0.24	8.79	0.21
Max	25.5	15.1	51.8	11.3
CV	93.8%	220.6%	91.9%	197.2%

<LOQ=below the limit of quantification (0.1 ng/mL)

The applicant noted, that this study confirmed the high inter-subject variability of the pharmacokinetics of granisetron overall and in both male and female cancer patients treated with oral granisetron and granisetron TDS. Median plasma concentrations at Visit 1 (anticipated peak plasma concentration) were higher for oral granisetron than granisetron TDS.

The CHMP noted that main PK data in patients were generated from two trials (8/C and 15/C). In Study 8/C minimally required time for patch application was 24 hours time before chemotherapy. In Study 392MD/15/C median time value prior to chemotherapy was 45.1 hours, median (SD) was 40.7 (9.4) hours, individual values ranged between 25 and 72 hours. So, median time value was closer to 48 hours than to 24 hours. As it can be seen from measured median plasma concentrations, differences between oral and TDS is ~ 7 times different in Study 8/C and ~4 times different in Study 15/C.

Population PK. The PK model was developed using data from 4/C, 8/C, 11/C, 15/C and 26/C. The objectives of the population PK analyses were to develop a population PK model for granisetron after granisetron TDS application and after oral administration, to explore the effects of various covariates on the PK characteristics of granisetron and to use it for PK/PD modelling.

Based on the granisetron TDS PK model for the cross-over study, the fraction, bioavailable after patch administration (F), was determined to be 46% relative to oral dosing. This value is based on the nominal dose. The median amount removed from the patch was 55% in trials 4/C, 8/C, 11/C and 26/C. It was assumed by the applicant that, based on the administrated dose, F is approximately *80% relative to oral*. As Granisetron exposures showed a high inter-individual variability, in the final PK model fitted to data of all granisetron TDS treated subjects, a *inter-subject CV of 112%* was determined for the apparent clearance (CL/F), which is inversely proportional to exposure. In the final model based only on the cross-over trial, an *intra-subject CV of 26%* was determined for exposure after granisetron TDS administration.

The CL/F of granisetron was estimated in both healthy subjects and patients after oral and granisetron TDS administration. This showed that CL/F in patients was decreased relative to healthy volunteers, by 75%

Distribution

Based on bibliographic data, granisetron is distributed with a mean volume of distribution of approximately 3 L/kg (Allen et al. 1995). Using the PopPK modelling, similar V values were obtained: mean V c = 322 L and Vss=468 L. This implies also certain accumulation.

Elimination

The mean plasma clearance in healthy subjects is reported as 0.79 L/h/kg (Allen et al. 1995[1]).

In Study 11/C and in the PPK modelling it could be observed that the apparent granisetron plasma half-life in healthy subjects was prolonged to approximately 36 hours due to the slow absorption rate of granisetron through the skin.

According to bibliographic data and in original studies evaluating CL after patch application (PPK modelling), the total plasma CL in healthy patients was ~0.79 l/h*kg or 42.5 L/hr and in patients CL = 23.6 L. This information is reflected in SmPC as "*in clinical studies conducted with SANCUSO, clearance in cancer patients was shown to be approximately half that of healthy subjects*".

In study 33/C, which was conducted to compare the metabolic profiles of granisetron (TDS and oral), and from plasma samples collected during Studies 11/C and 8C an analysis for metabolites from the patients treated with the TDS was performed.

Considering bibliographically data the result are reflected in the SmPC: Following an oral or IV dosing of granisetron approximately 10% of the dose is excreted unchanged with the remainder metabolised via hydroxylation or N-demethylation, with 7-hydroxylation the major route in humans.

Dose proportionality and time dependencies

No formal dose proportionality studies were performed. Some aspects relevant to dose determination were assessed in Study 11/C, where Granisetron TDS application resulted in maximal concentrations 48 hrs post application. Mean Cmax values of 1.15, 2.08 and 3.85 ng/mL and mean Cavg values of 0.68, 1.24, and 2.23 ng/mL were determined for 15 cm², 33 cm² and 52 cm² patch sizes, respectively

For the granisetron TDS, the mean area under the plasma concentration-time curve between time 0 and infinity (AUC0-∞) was 149, 287 and 420 ng.h/mL, for 15cm2, 33cm2 and 52cm2 patch, respectively. Average granisetron plasma concentrations and AUC(0-∞) increased proportionally with

[1] Allen, et al., 1995. The pharmacokinetics of granisetron, a 5-HT3 antagonist in healthy young and elderly subjects. Eur J Clin Pharmacol, 48(6), pp.519 – 520

granisetron TDS patch size (i.e. with dose). Terminal half-life of granisetron was similar for all three patch sizes with an overall mean of 33 hrs.

Intra- and inter-individual variability The main data for inter-subject variability was assessed in the relative bioavailability study (11/C). Inter-subject variability was comparable across the transdermal patch and oral granisetron treatments. The CV for AUC was 89% for the 52 cm2 granisetron TDS compared with 108% on Day 5 following oral dosing regimen. The coefficients of variation for Cmax values were 77% and 68% following patch or oral dosing respectively.

The CHMP acknowledged the high inter-subject and intra-subject variability of the main PK parameters (Cmax, Cavg, AUC, and CL).

Special populations

Gender. The gender effect was assed via bibliographic data and original studies (4/C, 26/C, 15/C and PPK modelling). Published data showed that Cmax is generally *higher in males* than in females but AUC is unaffected by gender. This seem broadly consistent with the findings in healthy subject study 4/C where the mean plasma granisetron Cmax and AUC in the healthy male subjects was greater than that seen in the females whilst in study 26/C, also in healthy subjects, the mean plasma granisetron Cmax and AUC were higher in females than males.

For Study 39/C, both granisetron TDS and i.v. granisetron exposure was *higher in females* compared to males, although there was considerable overlap in the ranges of individual values and high inter-subject variability.

The CHMP considered that overall there seem to be a general tendency towards higher concentrations in females in comparison to males, but this trend does not result in a clinical significant difference. This is also substantiated by the population pharmacokinetic model, where gender was not identified as a covariate improving the fit.

Race. Study SP-0101 assessed the PK of granisetron after a single 6-day application of granisetron TDS in healthy Japanese males. High inter-subject variability in systemic exposure was observed (as it is well documented for granisetron studies) but overall the PK profile in Japanese subjects was comparable to that in non-Japanese subjects.

Weight. Weight was assessed in study 40/C. Comparisons of mean Cmax, Cavg and AUC estimates indicated that systemic exposure appeared slightly lower in the normal subject group than in either the underweight or obese subject groups, although there was extensive overlap in the 95% CI around the geometric mean estimates for these parameters.

Elderly. Study 40/C specifically studied the PK profile of granisetron TDS in 24 elderly subjects versus a control group in younger subjects. The mean (± SD) ages for the control and elderly groups were: 30.8 (± 7.1) and 70.8 (± 5.0) years respectively. In the elderly group, 6 of the 24 subjects were ≥75 years old and the oldest subject was 84 years old. The results of the statistical analyses of the PK parameters Cmax, AUC(0−z), AUC(0−∞) and Cavg showed no significant differences at the 5% level between the age groups for any of the PK parameters.

Children. No study has been performed to assess granisetron TDS pharmacokinetics in children.

Impaired renal function. Urinary excretion of unchanged granisetron accounts for less than 20% of dose in healthy subjects following i.v. dosing. The rest of the dose administered is excreted 49% by urine and 34% by the faeces as metabolites, mainly 7-hydroxygranisetron. For this reason, dose adjustment in renal failure is considered unnecessary (Antonopoulos 2008[1], Clarke 1994[1]).

1 Antonopoulos, M.S & Caspi, A., 2008. Granisetron Transdermal Delivery Product

Additionally, total clearance of granisetron was not affected in patients with severe renal failure who received a single 40 µg/kg dose of granisetron (Carmichael et al 1989[2]).

Impaired hepatic function. Palmer (1994)[3] investigated the pharmacokinetics of granisetron in 20 cancer patients with malignant involvement of the liver and 19 cancer patients who did not have liver involvement. In this study total clearance was approximately halved compared to patients without liver involvement, which is expected due to the fact that granisetron is predominately eliminated by hepatic metabolism. For the reference product dose adjustment is not considered necessary based on the wide variability in PK parameters and good tolerance of doses above the recommended clinical dose. In section 4.4 of the SPC a special warning for hepatically impaired patients has been included considering the fact that granisetron is eliminated predominantly by the liver.

Pharmacokinetic interaction studies

In vitro

As reported in the literature (Bloomer et al. 1994[4]) and mentioned in the prescribing information of the reference product, granisetron does not induce or inhibit the cytochrome P-450 drug metabolizing enzyme system in vitro.

In vivo

The prescribing information of the reference product mentions that there have been no definitive drug-drug pharmacodynamic or PK interaction studies performed with i.v. granisetron; however safe administration is reported with drugs representing benzodiazepines, neuroleptics and anti-ulcer medications. Leigh et al. (1991, 1992)[5] report the results of two studies in 12 healthy subjects reviewing the effect of granisetron alone and in combination with lorazepam, and haloperidol, on psychometric performance, and for the latter on the electroencephalogram (EEG). The results of the studies suggested that granisetron had no impact on performance or the EEG and that it can be co-administered with the two agents without producing unwanted synergistic effects. Youlten (2004)[6] investigated the effect of repeat dosing with cimetidine on the pharmacokinetics of i.v. granisetron in 12 healthy subjects and found that PK parameters measured after cimetidine administration were not significantly different from those taken before.

Granisetron does not appear to interact with emetogenic cancer therapies. More recently Watanabe (2003)[7] suggested that granisetron neither inhibits nor induces the enzymes involved in paclitaxel and docetaxel metabolism. In a later study, Watanabe (2005)[8] similarly established that granisetron

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Profiler: Sancuso® (Granisetron Transdermal Delivery System) A New Formulation for Chemotherapy-Induced Nausea and Vomiting. P&T, 33(10), pp.1-27

1 Clarke, E. et al., 1994. Metabolism and disposition of 14C-granisetron in rat, dog and man after intravenous and oral dosing. Xenobiotica, 24, pp.1119-1131

2 Carmichael, J. et al., 1989. A pharmacokinetic study of granisetron (BRL 43694A), a selective 5- HT3 receptor antagonist: correlation with anti-emetic response. Cancer Chemother Pharmacol, 24, pp.45-49

3 Palmer, R., 1994. Efficacy and safety of granisetron (Kytril) in two special patient populations: children and adults with impaired hepatic function. Seminars in Oncology, 21(3), pp.22-25

4 Bloomer, JC, 1994. Characterisation of the cytochrome P450 enzymes involved in the in vitro metabolism of granisetron Br J Clin Pharmacol 38, pp. 557-566

5 Leigh, TJ, 1992. Effects of granisetron and haloperidol, alone and in combination on psychometric performance and the EEG Br J clin Pharmac 34, pp. 65-70

6 Youlten, L, 2004. The effect of repeat dosing with cimetidine on the pharmacokinetics of intravenous granisetron in healthy volunteers. JPP 56, pp. 160-175

7 Watanabe, Y, 2003. The effect of granisetron on in vitro metabolism of taclitaxel and docetaxel. The Cancer Journal 9/1, pp. 67-70

8 Watanabe, Y, 2005. The effect of granisetron on in vitro metabolism of dox0rubicin, irinotecan and etoposide. Current Medical Research and opinions 21/3, pp. 263-8

neither inhibits nor induces the enzymes involved in the metabolism of doxorubicin, irinotecan or etoposide.

Bloomer et al. (1994)[1] reported the inhibition of ring oxidation of ketoconazole in human microsomal studies, although the clinical significance of this is unknown. This is also the case for the results of a human PK study in which phenobarbital induction resulted in a 25% increase in total plasma clearance of i.v. granisetron (prescribing information originator).

Granisetron is metabolised by hepatic CYP3A4 and CYP1A1 enzymes, which is part of the cytochrome P450 enzyme system. Drugs that induce the CYP3A4 enzyme reduce serum concentration of granisetron or interacting drug, whereas drugs that inhibit CYP3A4 increase serum concentration of either drug.

In section 4.5 of the SmPC, the potential interaction with drugs that inhibit the isoenzyme CYP3A4 is discussed. Caution should be used when administering ketoconazole or phenobarbital concurrently with granisetron.

2.4.3. Pharmacodynamics

Mechanism of action

There are two sources of afferent input that can initiate the emetic reflex:

- abdominal vagal afferents with a variety of receptors, 5-HT_3, neurokinin-1, cholecystokinin-1, which are located in close proximity to enteroendocrine mucosal cells of the proximal small intestine. Antineoplastic agents stimulate these cells to release mediators that bind to the vagal fibers, and lead to an afferent stimulus that terminates in the dorsal brain stem.

- the area postrema (AP), a circumventricular structure located at the caudal end of the fourth ventricle. It is thought that gut-derived peptides and metabolites of chemotherapeutic agents induce emesis in part through binding at this site.

The 5-HT_3 receptors are in both central location (area postrema and nucleus tractus solitarius – NTS) and peripheral locations (vagal afferents) that are relevant to CINV. Substance P and endocannabinoids may also be relevant transmitters in CINV.

Primary and Secondary pharmacology

Granisetron is a selective antagonist of 5-hydroxytryptamine (5HT3 receptors). Pharmacological studies have demonstrated that granisetron is effective against nausea and vomiting as a result of cytostatic therapy. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types, including 5HT1, 5HT2, 5HT4 and dopamine D2 binding sites.

The following pharmacology assessmentshave been performed specific for the present application.

Study 392MD/39/C. This was a Phase 1, single-site, single-blind (except for the use of moxifloxacin), randomized, placebo- and positive-controlled, 4-arm parallel study with the primary objective to evaluate the effect of doses of granisetron TDS (52 cm2) and i.v. granisetron on the interval from start of Q wave to end of T wave (QT) in 120 healthy male and 120 healthy female subjects, who were in good health as determined by a physician, aged between 18 to 50 years inclusive, weighed at least 50 kg (110 pounds), had a body mass index of 18-32 kg/m2 inclusive.

[1] Bloomer, JC, 1994. Characterisation of the cytochrome P450 enzymes involved in the in vitro metabolism of granisetron Br J Clin Pharmacol 38, pp. 557-566

No clinically significant effect of the granisetron TDS was observed on ECG parameters (heart rhythm, PR interval or QRS intervals), on the derived ECG parameters (QTcF, QTcB, and QTcI), or on the incidence of ST-segment and T-wave abnormalities. The upper limit of all the one-sided 95% confidence intervals for the time-matched granisetron TDS versus placebo analyses was below 10 msec. There were no extreme QTcF value changes > 60 msec.

The results resembles findings of gender differences ~ 50 % higher of AUC and Cmax in females, observed in study 26/C.

PK/PD modelling. A PK/PD model was developed using PK data from studies 4/C, 8/C, 11/C, 392MD/15/C and 26/C and PD data from study 15/C (see information above). *General methodology.* The model applied to describe the PK and PD was a population or mixed-effect models. *Modelling strategy.* A sequential PK-PD modelling approached was followed. First, the oral PK model was developed. Subsequently the distribution and elimination parameters from this oral model were used in the development of the PK model for patch administration. The PK models were then used for the investigation of the PK-PD relationship. *Development of a PK-PD model.* The final PK models developed for patients after oral dosing or patch application were used to derive the exposure of each individual to granisetron in the Study 15/C. From the *post hoc* estimates, exposure was calculated in NONMEM as the area under the curve (AUC) from the start of chemotherapy until 24 h later (AUC24), and the AUC from start of patch attachment or oral dosing until the end of the study period, which is 7 days later (AUC168). Possible exposure-response relationships were evaluated using *proportional odds models*. The relationship between AUC24 and Total Control on Day 1 was evaluated in separate models after oral administration, patch application, and in a combined oral/patch model. In an analogous manner, the relationship between AUC168 and Total Control Overall was evaluated.

Results: In Study 15C plasma granisetron concentrations were determined at two time points (Visit 1 and Visit 6). An exposure-dependent effect on TC could not be detected using PK-PD modelling, for none of the exposure-response relationships.

2.4.4. Discussion on clinical pharmacology

Granisetron TDS has been developed for the prevention of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy for up to 5 consecutive days. The clinical development strategies were designed to bridge to the previous findings of efficacy and safety for the reference product, the oral formulation of granisetron, to the transdermal formulation. The pharmacology program performed is formally acceptable for this purpose.

A dose ranging and comparative bioavailability study with oral granisetron (392MD/11/C) showed that a 52 cm2 patch was the most suitable for further clinical development. The calculated flux of granisetron from grainsetron TDS 52 cm² is 3.1 mg/24 h. Pharmacological characteristics of the patch showed that initially plasma concentrations were slow to increase and that Cmax was reached at around 48 hours. Mean Cmax with granisetron TDS (3.85 ng/mL) was lower than that measured with oral granisetron 2 mg (5.5 ng/mL). However, the delivered dose from granisetron TDS resulted in an average plasma granisetron concentration (Cavg) of 2.23 ng/mL compared with 2.14 ng/mL after the first oral granisetron administration and 2.6 ng/mL following the final oral granisetron dose. When administered for 7 days the granisetron TDS 52 cm2 patch delivers, on average, a dose of 3.1 mg of granisetron per day. Hence the granisetron TDS 52 cm² patch delivers comparable average plasma concentrations to 2 mg oral granisetron every 24 hours. Therapeutically relevant concentrations were maintained through to the removal of the patch at 144 hrs (Day 6), with less fluctuation in comparison with repeat daily oral administration. Upon removal of the patch plasma concentrations continued to decline slowly, suggesting a dermal reservoir of drug.Consistent with PK studies of other formulations the interpatient variability of granisetron concentrations and exposure is high. Available data showed

that granisetron TDS pharmacokinetics are not affected by external heat, body fat or age. Population PK analysis of data from clinical studies showed that granisetron PK are not affected by renal impairment and gender. It is likely that the apparent gender differences are due to the high variability of granisetron pharmacokinetics

In Study 392MD/15/C median time value prior to chemotherapy was 45.1 hours, median (SD) was 40.7 (9.4) hours, individual values ranged between 25 and 72 hours. So, median time value was closer to 48 hours than to 24 hours. Median plasma concentrations at Visit 1 (anticipated peak plasma concentration) were higher for oral granisetron than granisetron TDS.

It is important to have sustained exposure to granisetron over the whole time course of chemotherapy however considering that there is no established relationship between granisetron levels and control of CINV, the high degree of variability is not thought clinically relevant for control of CINV.

2.4.5. Conclusions on clinical pharmacology

Pharmacological characteristics of the patch showed that initially plasma concentrations were slow to increase and that Cmax was reached at around 48 hours. Granisetron TDS 52 cm² patch delivers mean plasma concentrations comparable to 2 mg oral granisetron every 24 hours However a lower median plasma concentration with regards to the tablet was observed at Visit 1 (Day 1).

It is important that at the start of emetic chemotherapy, patients have sufficient exposure to granisetron to prevent nausea and vomiting and that this exposure is sustained over the time course of chemotherapy. Plasma levels of granisetron are poorly correlated with efficacy, however, in the absence of measurements of concentrations at the receptor level they are the best surrogate available to indicate that sufficient exposure to granisetron has been achieved to be of therapeutic benefit.

Granisetron TDS 52 cm² patch delivers mean plasma concentrations comparable to 2 mg oral granisetron every 24 hours However a lower median plasma concentration with regards to the tablet was observed at Visit 1(Day 1).The performed studies provided the rational for therapeutic dosage and application time (starting at least 24-48 hours before chemotherapy and lasting for 7 days). The lower plasma concentrations at D1 and a possible slower onset of efficacy is reflected in the restriction of the indication to patients with swallowing difficulties and in 5.1. of the SmPC.

2.5. Clinical efficacy

The applicant submitted results of two comparative efficacy studies. Both of these used a 2 mg oral granisetron dose as an active comparator. For details see "Tabular Overview of Clinical Studies".

2.5.1. Dose response studies

No formal dose response studies were submitted. The rationale for the choice of the dose is based on the results from the clinical PK study 11/C (see section 2.4.2 for details).

2.5.2. Main study

Study 392MD/15/C

A Randomised, Active Control, Double-Blind, Double-Dummy, Parallel-Group, Multi-National Study to Assess the Efficacy, Tolerability and Safety of the Granisetron Transdermal Delivery System in Chemotherapy-Induced Nausea and Vomiting (CINV) Associated With the Administration of Moderately or Highly Emetogenic Multi-Day Chemotherapy

Methods

Study Participants

Main inclusion criteria: (1) Male or female aged; ≥ 18 yrs for the Czech Republic and Russia; ≥ 16 yrs for Serbia and Montenegro; ≥ 15 yrs for Bulgaria, India, Mexico, Poland, Romania and the USA (no upper limit) (2) Histologically and/or cytologically confirmed cancer and an Eastern Cooperative Oncology Group (ECOG) status of ≤ 2. (3) Life expectancy of ≥ 3 months; (4) Assigned to receive the first cycle of a new multi-day MEC or HEC regimen including the daily administration of a cytotoxic regimen with the emetogenic potential of level 3-5 (Hesketh 1997) for 3-5 days.

Main exclusion criteria: (i) hypersensitivity to adhesive plasters; (ii) contraindications to 5-HT3 receptor antagonists; (iii)any cause for nausea and vomiting other than CINV (iii) any episode of retching, vomiting or uncontrolled nausea in the 72 hour period prior to chemotherapy administration; (iv) clinically relevant abnormal electrocardiogram (ECG) parameters (at the discretion of the investigator) and/or a baseline QT corrected for heart beat (QTc) > 450 ms for male patients or a baseline QTc > 470 ms for female patients; (v) Other 5-HT3, neurokinin-1 (NK1) or dopamine antagonists.

Treatments

Treatments Patients were randomly allocated to one of two treatment groups at a 1:1 ratio: (i) GTDS + placebo capsule; (ii) placebo patch + active capsule (2 mg oral granisetron). The patch was applied 1-2 days prior to the first dose of MEC or HEC and remained in place for a full 7 days in all patients (e.g. Saturday 7 pm to Saturday 7 pm). The capsule was administered 1 h prior to MEC or HEC on each day the HEC or MEC cytotoxic agent or combination of cytotoxics was administered.

Prior and concomitant therapy. Some of the treatments were considered as criteria for exclusion due to violations of the protocol, depending on when the concomitant medication was administered: (i) concomitant radiotherapy of total body, brain or upper abdomen within one week of study entry or planned during the study; (ii) intake of medication to control the symptoms of a brain tumour, brain metastasis or seizure disorder; (iii) patients using SSRI antidepressants (unless a stable dose for the duration of the study); (iv) scheduled to receive an neurotising NK1 receptor antagonist, dopamine receptor antagonist or another 5-HT3 receptor antagonist between 72 h prior to the administration of the chemotherapy and patch removal

Concomitant use of corticosteroids The concomitant use of prophylactic corticosteroids was permitted throughout the study according to local clinical practice.

Rescue Medication. The investigator was permitted to prescribe rescue medication, in accordance with the site's standard of care, to be taken by the patient, as required. There were no restrictions on the use of anti-emetic drugs as rescue medication except those known to cause prolongation of QTc. Patients recorded details of the medication taken, including time, in their diary card.

Objectives

The null hypothesis was that granisetron TDS was inferior to oral granisetron.

Non-inferiority margin. The applicant employed delta for Non-inferiority margin as 15%.

The applicant justified the chosen NI margin for multiday type CINV as follows:

(1) The historical evidences for efficacy, including the effect of intravenous 5-HT3-RA plus dexamethasone in multiday type of CINV (3 to 5 days of cisplatin administration) as shown during MASCC Perugia 2004 Consensus conference.

(2) Clinical judgement of the scientific advisory board.

(3) Superiority of the reference product over placebo: numerical difference is estimated from 24% to 35%.

(4). Additive effect of dexamethasone. The argumentation is based on (i) an estimated minimum relative value for granisetron TDS (~7%) that is falling within chosen 15% of NI margin and (ii) similar to 15/C study design approach taken in previous study for palonsetron authorisation.

The 2-sided 95% confidence interval of difference was obtained via a logistic regression, adjusting for study treatment, gender, planned duration of chemotherapy regimen (3, 4/5 days), planned cisplatin/corticosteroid use, and chemotherapy naive status (yes, no) as recorded in IVRS (called "planned chemotherapy naivety"). A main effects model was used.

Outcomes/endpoints

The primary endpoint of the trial was the composite endpoint complete control (CC) of CINV over the whole period at risk from the first dose of chemotherapy to 24 hours after the last dose of chemotherapy (3, 4 or 5 days). CC was defined in study 15/C as no vomiting and/or retching, no more than mild nausea and no rescue medication.

The main secondary efficacy endpoints were: (i) time from start of MEC or HEC to treatment failure (failure of CC); (ii) time from start of MEC or HEC to treatment failure (failure of CR, i.e. no vomiting and/or retching and no rescue medication); (iii) time from start of MEC or HEC to first administration of rescue medication; (iv) time from start of MEC or HEC to first emetic episode (vomiting/retching); (v) Time from start of MEC or HEC to first episode of more than mild nausea; (vi) Percentage of patients achieving CC of CINV overall and during different time periods.

Sample size

The sample size for this study was based on efficacy considerations. In particular, it was based upon the primary efficacy endpoint: the percentage of patients achieving CC of CINV during the period (from the first administration until 24 h after the last administration of ME or HE multi day chemotherapy).

The null hypothesis was that the TDS is inferior to oral granisetron. The alternative hypothesis was that the TDS is not inferior (by greater than a non-inferiority margin Δ) to oral granisetron.

The hypothesis was tested via construction of a two-sided 95% confidence interval around the difference in percentage CC between the 2 treatment groups (D). If the lower limit of this confidence interval was greater than -Δ, the null hypothesis was rejected.

Setting the reference rate for CC with oral granisetron to 50%, an absolute non-inferiority margin of 15%, and 90% power, 576 patients (288 per group) were required. This assumed that there was no clinical difference (i.e. D=0) between oral granisetron and GTDS. This sample number was conservative in the sense that it was based on the CC rate for oral granisetron which gave the highest required sample size. However, it did not allow for an interstratum difference in effect size. Analysis of the primary endpoint was carried out on both the FAS and the PPS. As the PPS was likely to be smaller than the FAS and assuming 9% drop out, based on the GTDS Phase II study, the randomisation of approximately 630 patients in all (315 per treatment group), yielding a PPS of 576 patients, was planned.

Randomisation

Once patients were confirmed as eligible for the study and had completed all screening procedures, they were each assigned a unique randomisation number by a centralized randomisation procedure using Interactive Voice Response System (IVRS). After randomisation, the patient received a unique blinded number, allocated by the IVRS, corresponding to the patient's randomised treatment group. After matching the appropriate patient pack with the patient pack number, in accordance with the IVRS, patients were dispensed medication by the investigator or the designee. The patient pack number was entered in the CRF. A randomisation list was generated independently by a statistician, not involved in the conduct or management of the study, using the validated computer programme SAS, Version 8.02.

A random permuted block design was used to obtain a 1:1 ratio with categories using the following stratification variables:

• Gender

• Chemotherapy regimen:

1. Cisplatin chemotherapy regimen,

2. Non-cisplatin chemotherapy regimen with planned use of corticosteroids

3. Non-cisplatin chemotherapy regimen without planned use of corticosteroids

• Duration of planned chemotherapy (3 day versus 4/5 day)

• Chemotherapy naive versus non-naive

Blinding (masking)

A double-dummy method was used to ensure blinding. Each patient received a patch (active or placebo) and an appropriate number of capsules (active or placebo). The patches containing granisetron and patches without granisetron were of identical appearance, as were the capsules containing granisetron and placebo capsules.

The investigator did not break the treatment code unless knowledge of the patient's treatment was required for the patient's clinical care and safety. If unblinding was considered necessary the respective patient was withdrawn from the study after unblinding.

Statistical methods

Study populations. Several populations for statistical analysis were defined for this study. *Full Analysis Set*. The Full Analysis Set (FAST) was defined as all randomised patients who received study treatment (GTDS or capsule) and had at least one efficacy assessment after the start of chemotherapy. *Per Protocol Set.* The Per Protocol Set (PPS) was defined as all FAST patients without violations of the protocol which directly impinged on or affected the primary endpoint. *Safety Set.* The Safety Set (SS) was defined as all patients who received at least one dose of study treatment (GTDS or capsule).

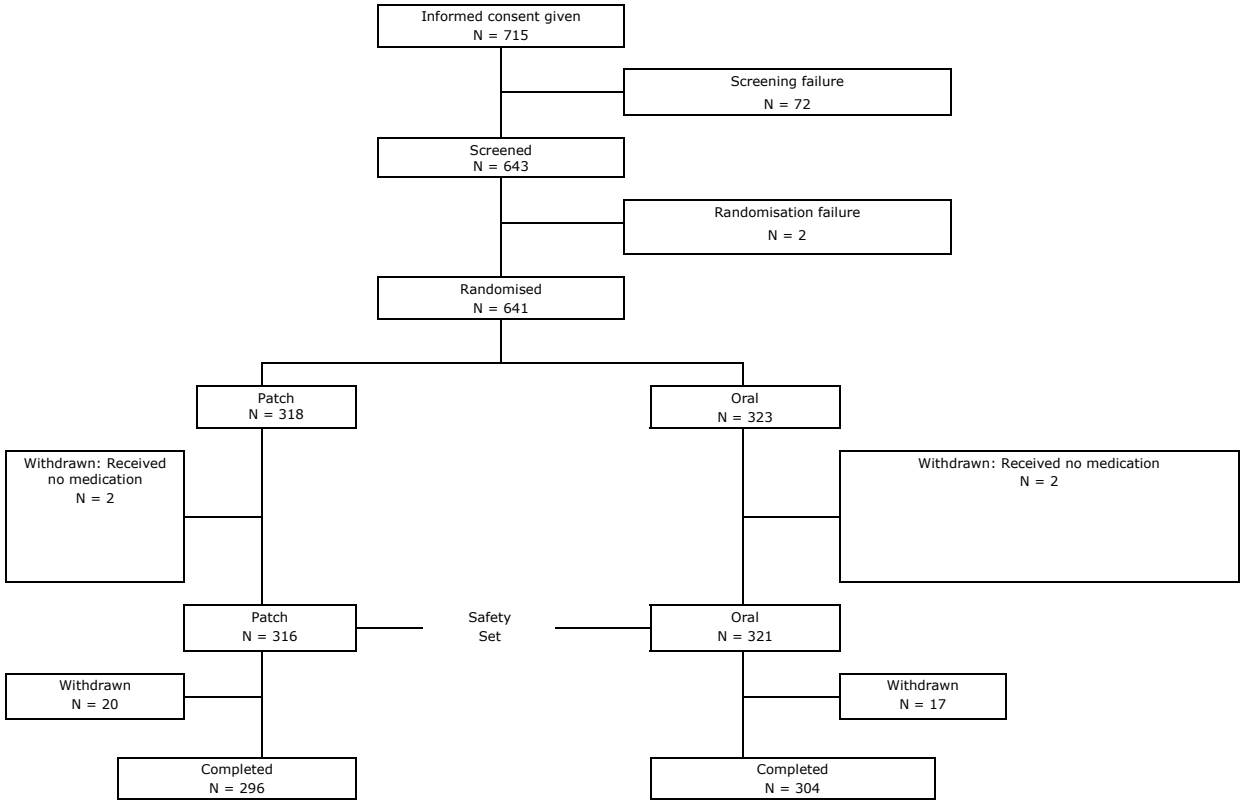
Handling of outliers and missing data. Missing data were not imputed, except for the analysis of efficacy endpoints, where the following assumptions were made: (i) If severity of event was missing the worse case was assumed; (ii) If time of event/rescue medication was missing but the date corresponded to a chemotherapy day then the time was set to 1 minute (min) after start of that day's chemotherapy; (iii) Nausea and vomiting starting prior to the first chemotherapy on day 1 were

ignored; (iv) Patients who withdrew from the study during the primary endpoint evaluation period were assumed not to have attained the primary endpoint (i.e. not achieved CC).

Results

Participant flow

Figure 12: Disposition of Patients in Study 15/C



A total of 39 patients (24 patients in the GTDS group and 15 patients in the oral group) from the FAS were excluded from the PPS due to protocol violations.

Recruitment

First patient enrolled: 24 January 2006
Last patient completed: 11 October 2006

Conduct of the study

Several amendments were introduced (i) Country-Specific Amendment 1 as requested by local Regulatory Authorities (exclude minors in some countries), (ii) Global Amendment 1 as requested by the FDA (mainly introducing the aspects of QT prolongation measurements), and (iii) changes in SAP (main of them – changing the definition of „overall emetogenicity" from average to maximal observed; primary endpoint results was examined not via an *unadjusted logistic regression*. but the normal *approximation to the binomial*.) (iv) additional changes before unblinding (omitting metabolites analysis [due to unavailability of validated methods], method of tabulation of TEAE, omitting capturing prior CINV); (v) Additional changes post unblinding (as some subjects had been incorrectly included/excluded from the PPS. This was corrected post unblinding and all affected tables, figures and listings were re-run).

Baseline data

Demographics. Demography data show that patient where comparable within groups, with regards to age group, weight, height, BMI and ethnic origin. Patients where comparable also with regards to nicotine and alcohol use as well as ECOG performance status.

Disease characteristics.

	Granisetron TDS (N = 308)		**Oral Granisetron (N = 313)**	
	n	%	n	%
History of radiotherapy				
Yes	61	20	65	21
No	247	80	248	79
Missing	0	0	0	0
If yes, number of previous radiotherapy courses				
1	32	10	39	12
2	8	3	5	2
3+	18	6	19	6
Missing	3	1	2	1
History of chemotherapy				
Yes	87	28	94	30
No	221	72	219	70
Missing	0	0	0	0
If yes, number of previous chemotherapy courses				
1	34	11	46	15
2	14	5	13	4
3+	39	13	35	11
Missing	0	0	0	0

Individual data on medical history, related to primary disease reveal that in general primary tumour sites were comparable. More then 40 % had metastatic disease. The history of disease therapy for the treatment groups was comparable with regards to history of radiotherapy, number of curses; history of chemotherapy and number of previous courses. The most common *past relevant medical conditions* were comparable by system – organ class.

	Granisetron TDS (N = 308)		**Oral Granisetron (N = 313)**	
	n	%	n	%
History of radiotherapy				
Yes	61	20	65	21
No	247	80	248	79
Missing	0	0	0	0
If yes, number of previous radiotherapy courses				
1	32	10	39	12
2	8	3	5	2
3+	18	6	19	6
Missing	3	1	2	1
History of chemotherapy				
Yes	87	28	94	30
No	221	72	219	70
Missing	0	0	0	0
If yes, number of previous chemotherapy courses				
1	34	11	46	15

2	14	5	13	4
3+	39	13	35	11
Missing	0	0	0	0

Primary disease.

There was a broad range of primary disease. Pro-emetogenic primary diseases (i.e. Gastrointestinal and gynaecological malignancies) were balanced in both treatment arms. Pro-emetogenicity of CNS metastases was not captured however it was acknowledged by the CHMP that this influence might be minor due to defined exclusion criteria (any condition likely to cause nausea and vomiting other than CINV), randomization and short duration to efficacy assessment (5 days).

	Granisetron TDS (N = 308)		**Oral Granisetron (N = 313)**	
	n	**%**	**n**	**%**
Primary tumour site				
Gynaecological	68	22	61	19
Lung	64	21	64	20
Head/neck	38	12	33	11
Breast	30	10	36	12
Gastrointestinal	27	9	26	8
Genitourinary	24	8	23	7
Lymphoma	19	6	32	10
Melanoma	11	4	5	2
Leukaemia	10	3	17	5
Sarcoma	8	3	6	2
Multiple myeloma	2	1	3	1
Brain	1	< 1	1	< 1
Unknown	4	1	6	2
Missing	2	1	0	0
Metastatic disease				
Yes	136	44	129	41
No	171	56	184	59
Missing	1	< 1	0	0

Chemotherapy and their emetogenicity.

An external expert classified the 159 unique regimens applied in the pivotal study into 28 sets (15 HEC and 13 MEC regimens) which were equally balanced in the oral and the TDS group. The algorithm to calculate the emetogenicity for combination chemotherapy was proposed as published by Hesketh (1997)[1]. This algorithm was introduced prior to unblinding into this study as the amendment following expert advice. The CHMP considered the Hesketh score as informative for the regulatory purpose for this application.

Table 30 (section 10 Table 1): Maximum Hesketh level, Study 15/C

Section 10 Table 1: Maximum Hesketh level by day split by actual duration of original ME or HE chemotherapy (Full Analysis Set)

		1 or 2 day regimen				3 day regimen				4 day regimen				5 day regimen			
		Patch		Oral		Patch		Oral		Patch		Oral		Patch		Oral	
	Hesketh	(N = 6)		(N = 4)		(N = 204)		(N = 209)		(N = 17)		(N = 18)		(N = 81)		(N = 82)	
	Level	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Day 1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	0	1	25	0	0	1	< 1	1	6	1	6	0	0	0	0
	3	0	0	0	0	9	4	13	6	6	35	5	28	5	6	2	2
	4	0	0	2	50	38	19	55	26	1	6	1	6	14	17	16	20
	5	6	100	1	25	157	77	140	67	9	53	11	61	62	77	64	78
Day 2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	2	33	1	25	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	19	9	20	10	3	18	1	6	18	22	16	20
	4	0	0	1	25	83	41	101	48	4	24	6	33	9	11	8	10
	5	0	0	2	50	102	50	88	42	10	59	11	61	54	67	58	71
Day 3	1	-	-	-	-	0	0	0	0	0	0	0	0	0	0	0	0
	2	2	33	1	25	0	0	0	0	0	0	0	0	0	0	0	0
	3	-	-	-	-	19	9	21	10	3	18	1	6	19	23	18	22
	4	-	-	1	25	94	46	113	54	4	24	5	28	9	11	8	10
	5	-	-	-	-	91	45	75	36	10	59	12	67	53	65	56	68

[1] Hesketh, P.J., et al. 1997. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol, 15(1), pp.103-109

Day 4	1	-	-	-	-	-	-	-	-	0	0	0	0	0	0	0	0
	2	-	-	-	-	13	6	10	5	0	0	0	0	0	0	0	0
	3	-	-	-	-	-	-	-	-	3	18	1	6	21	26	19	23
	4	-	-	1	25	-	-	1	< 1	5	29	5	28	13	16	13	16
	5	-	-	-	-	-	-	-	-	9	53	12	67	47	58	50	61
Day 5	1	-	-	-	-	-	-	-	-	4	24	5	28	0	0	0	0
	2	-	-	-	-	6	3	7	3	2	12	2	11	0	0	0	0
	3	-	-	-	-	-	-	-	-	-	-	-	-	21	26	20	24
	4	-	-	1	25	-	-	-	-	-	-	-	-	13	16	15	18
	5	-	-	-	-	-	-	-	-	1	6	1	6	47	58	47	57
Original																	
Overall	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Max.	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	0	0	0	0	8	4	12	6	3	18	1	6	5	6	2	2
	4	0	0	2	50	38	19	56	27	4	24	4	22	14	17	16	20
	5	6	100	2	50	158	77	141	67	10	59	13	72	62	77	64	78

Source: Appendix B-1.1, Table 2.6.2.1
Note: Some patients did not start ME or HE chemotherapy until day 2. Patient 1070328 did not have chemotherapy on Day 3 (but with grades of 4, 5, 4, 4 for days 1, 2, 4 and 5 respectively) and is considered as having a 2 day regimen.
[1] Overall emetogenicity: Moderate if maximum Hesketh across days is 3 or 4, High if maximum Hesketh across days is > 4
HE/ME: highly/moderately emetogenic
N: Number of randomised patients in the respective treatment group
n: Number of patients with data available
%: percentage based on N

Concomitant medication. The use of antiemetogenic concomitant medicines was slightly higher in the TDS group (up to 12- 13%, firstly for propulsives, antihistamines, and benzodiazepines).

Concomitant corticosteroid use was comparable between groups (median dosage was 8 and 7.5 mg of dexamethasone equivalent per day). Of the 621 patients included in the Full Analysis Set (FAS), 396 were also administered corticosteroids. As anticipated the use of corticosteroids with cisplatin was high (277/446 = 62.1%) and stratification according to cisplatin use helped ensure that the use of corticosteroids overall in the study was balanced between the two groups (oral: 201 patients; granisetron TDS: 195 patients). The majority of patients used them not as rescue medications. The use of non-rescue concomitant therapy was comparable between both treatments groups.

Table 28: Dexamethasone Equivalent Doses[a] Across Both Arms Study 392MD/15/C (FASt)

Treatment Group		Average Dexamethasone Equivalent Dose per Day During Chemotherapy
Granisetron TDS	Total patients	308 mg
	Number with any CS	188 mg
	Median[b]	***8.0 mg***
	Minimum	0.0
	Maximum	207.0 mg
Oral	Total patients	313 mg
	Number with any CS	193 mg
	Median	***7.5 mg***
	Minimum	0.0
	Maximum	828.0 mg

The corticosteroid use was analysed for the Full analysis set. All corticosteroids used during the 24 hours prior to the start of chemotherapy and during days on which chemotherapy was given were included, unless identified in the case report form as 'rescue medication'. Corticosteroids with a respiratory indication are excluded (4 patients).; a: British National Formulary, 2007 ; b: Patients who received no CS are included as zero dose in the median, minimum and maximum

Treatment compliance and patch adhesion. The majority of patients (~76%) in both treatment groups had the patch on for 7 days and most of the patients (~90%) for primary evaluation had taken a capsule for the correct number of days.

Numbers analysed

Overall 715 patients were screened to yield 621 in the FAS and 582 in the PPS. The disposition of the patients is depicted in Table 21 and Figure 12.

Table 21: Analysis Sets (All Randomized Patients, Study 15/C)

	Patch (N = 318)		Oral (N = 323)		All (N = 641)	
	n	%	n	%	n	%
Safety Set (SS)[1]	316		321		637	
Full Analysis Set (FAS)	308	96.9	313	96.9	621	96.9
Per Protocol Set (PPS)	284	89.3	298	92.3	582	90.8

Source: Appendix B-1.1, Table 1.3
[1] The numbers of patients are by treatment received
n: Number of patients with data available
%: Percentage based on number of randomised patients

Outcomes and estimation

Primary Endpoint (Complete Control)

In the ***PPS*** population the percentage of patients who achieved CC from the first administration until 24 hours after the start of the last day's administration of the MEC or HEC regimen was comparable between granisetron TDS and the oral groups with the point estimate of the difference between groups of –4.89% (95% CI–12.91%; 3.15).

Since the lower limit of this confidence interval was above –15%, the null hypothesis was rejected and the alternative hypothesis was accepted, i.e. that granisetron TDS was non-inferior to oral granisetron.

The results of the supportive analysis of the primary endpoint on the ***FAS*** were similar to the results obtained for the PPS (see Table 32). The percentage of patients achieving complete control was comparable between the two treatment groups.

Table 32: Primary Efficacy Endpoint – Study 392MD/15/C Complete Control (Adjusted Logistic Regression) PPS and FAS

Per Protocol Set	**Granisetron TDS (N = 284)**		**Oral Granisetron (N = 298)**		**Adjusted Logistic Regression[a] Difference (%)**	
	n	**%**	**n**	**%**	**Estimate**	**95% CI**
Complete Control						
Yes	171	60.2	193	64.8	-4.89	-12.91, 3.13
No	113	39.8	105	35.2		
Full Analysis Set	**Granisetron TDS (N = 308)**		**Oral Granisetron (N = 313)**		**Adjusted Logistic Regression[a] Difference (%)**	
	n	**%**	**n**	**%**	**Estimate**	**95% CI**
Complete Control						
Yes	185	60.1	205	65.5	-5.77	-13.51, 1.97
No	123	39.9	108	34.5		

Source: **Study 392MD/15/C;** a:Primary comparison estimated via a logistic regression model, adjusting for treatment, gender, planned cisplatin and corticosteroid use, planned regimen duration and chemotherapy naivety as recorded in IVRS.; CI=confidence interval; N=Number of randomised patients in the respective treatment group; n=Number of patients; %=Percentage based on N

The CHMP noted that only one cycle of chemotherapy was included in the pivotal study 392MD/15/C, and therefore the activity during further cycles of chemotherapy is unknown. The applicant explained that is not seeking specific wording in the indication relating to use over multiple cycles. This was acknowledged by the CHMP and included in 5.1 of the SmPC.

Secondary Endpoints. A number of secondary efficacy analyses revealed similar differences in secondary efficacy assessment including the estimated point differences as assessed via complete response and total control ranging from -3.8% to -6.58% for PPS population and from -4.5% to -7.74% for FAST population (see Table 36). The lower bound of the 95% CI was below settled delta of 15% only in one case – CR in FAST and above -15% for all the rest response analyses.

Table 36: Efficacy Endpoints (Adjusted Logistic Regression for CC, CR)[1] Study 15/C

Group	Estimated Point Difference	95% Confidence Interval
Per Protocol Set (n=582)		
Complete Control[a]	-4.89% (granisetron TDS 60.2 %, oral 64.8 %)	-12.91%, +3.1 %
Complete Response[b]	-6.58% (granisetron TDS 62.0%, oral 68.1%)	-14.43%, +1.27%
Total Control[c]	-3.8% (granisetron TDS 55.6%, oral 59.4%)	-11.8%, +4.3%
Full Analysis Set (n=621)		
Complete Control[a]	-5.77% (granisetron TDS 60.1%, oral 65.5%)	-13.51%, +1.97%
Complete Response[b]	-7.74% (granisetron TDS 61.7%, oral 69.0%)	-15.30%, -0.18%
Total Control[c]	-4.5% (granisetron TDS 55.8 %, oral 60.4%)	-12.3%, +3.2%

a: Complete Control: no vomiting, no more than mild nausea, no rescue medication; b: Complete Response: no vomiting, no rescue medication
c: Total Control: no vomiting, no nausea, no rescue medication ; [1]The differences presented in this table for TC are absolute differences between the percentages in the treatment groups, and the confidence intervals are based on the normal approximation to the binomial

The efficacy analysis by Day showed results consistent with the overall non-inferiority conclusion of the primary analysis. On Day 1, the estimated point difference was –4.89%; 95% confidence interval (-12.91%, +3.13%) for the PPS. Although the estimated difference between the means for CC is greatest on Day 1 the lower bound of the 95% CI remains above -15%, demonstrating consistency with the primary efficacy endpoint.

Figure 14: Difference in Control by Day (FAST, All Patients); CC: Complete Control (Primary Endpoint Included for Comparison) Study 15/C

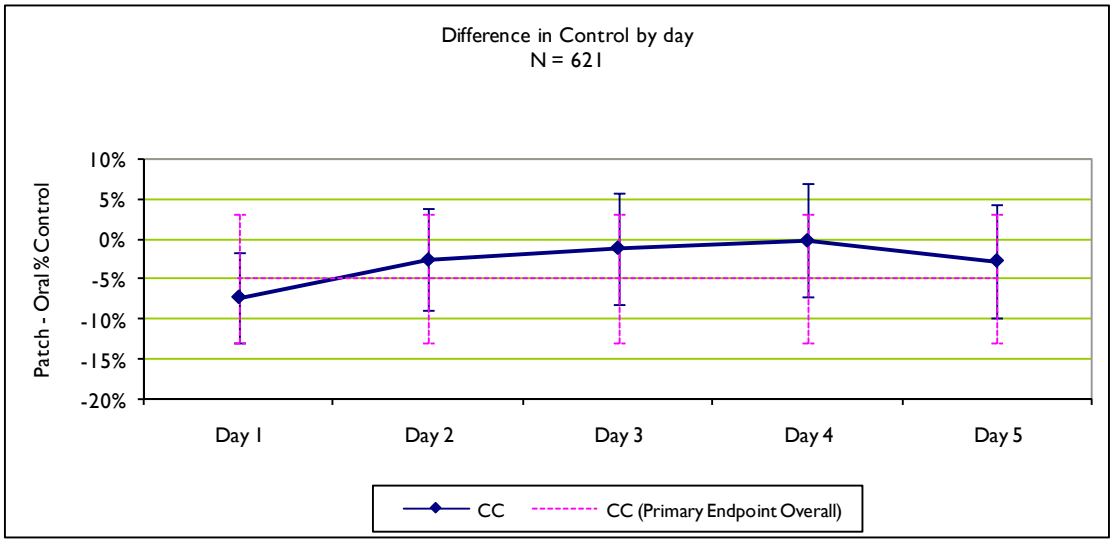


Table 37 (30): percentage of patients achieving complete control overall and by day (FAS) Study 15/C

Table 30: Percentage of patients achieving complete control overall and by day (Full Analysis Set)

	Planned 3-day course					
	Patch (N = 202)			Oral (N = 201)		
	N*	n	%	N*	n	%
Day 1	200	161	80.5	201	175	87.1
Day 2	199	156	78.4	200	160	80.0
Day 3	198	142	71.7	200	142	71.0
Day 4	174	139	79.9	170	134	78.8
Day 5	163	140	85.9	163	140	85.9
During PEEP	202	123	60.9	201	133	66.2
Overall	182	91	50.0	173	88	50.9
	Planned 4/5-day course					
	Patch (N = 106)			Oral (N = 112)		
	N*	n	%	N*	n	%
Day 1	105	89	84.8	112	102	91.1
Day 2	106	84	79.3	112	92	82.1
Day 3	105	81	77.1	112	88	78.6
Day 4	105	79	75.2	112	88	78.6
Day 5	101	79	78.2	107	91	85.1
During PEEP	106	62	58.5	112	72	64.3
Overall	104	58	55.8	108	68	63.0

Source: Appendix B-1.2.9, Table 3.10.1 and Table 3.10.2
PEEP: primary endpoint evaluation period,
N: Number of patients in the respective treatment group
N*: Number of patients with data available
n: Number of patients
%: Percentage based on N*

The CHMP noted that since non inferiority was shown for the primary endpoint, and the endpoints are all related, it is not surprising that the small, non significant difference of –4.89% observed in the primary endpoint between the TDS and oral groups was generally apparent across the secondary endpoints.

Day 1 and overall (up to Day 5) treatment failure calculations.

The applicant presented clearly positioned composition of treatment failures on Day 1 (see Table below).

Table 1: Percentages of Patients Achieving CC, CR, Requiring Rescue Medication or Experiencing More than Mild Nausea or Vomiting/Retching (FAS)

3-day course planned N = 403	During PEEP		Overall		Day 1		Day 2		Day 3		Day 4		Day 5	
Endpoint	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral
Complete Control (CSR Table 30)	60.9%	66.2%	50.0%	50.9%	80.5%	87.1%	78.4%	80.0%	71.7%	71.0%	79.9%	78.8%	85.9%	85.9%
Complete Response (CSR Table 34)	62.9%	69.7%	53.6%	55.8%	82.0%	88.1%	80.4%	82.0%	72.7%	75.5%	82.2%	80.0%	87.1%	88.3%
Requiring rescue medication (CSRTable 35)	16.8%	13.9%	25.9%	21.7%	8.4%	3.5%	8.5%	7.5%	8.0%	8.5%	9.7%	6.5%	5.5%	4.3%
Vomiting or retching (CSR Table 36)	34.5%	27.0%	43.2%	39.4%	16.0%	9.5%	15.7%	16.5%	22.8%	22.0%	11.9%	16.5%	7.6%	8.6%
More than mild nausea (CSR Table 37)	16.8%	16.6%	24.9%	23.4%	6.6%	6.0%	9.1%	7.5%	13.3%	12.1%	8.3%	7.7%	3.8%	4.3%

4/5-day course planned N = 218	During PEEP		Overall		Day 1		Day 2		Day 3		Day 4		Day 5	
Endpoint	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral	Patch	Oral
Complete Control (CSR Table 30)	58.5%	64.3%	55.8%	63.0%	84.8%	91.1%	79.3%	82.1%	77.1%	78.6%	75.2%	78.6%	78.2%	85.1%
Complete Response (CSR Table 34)	59.4%	67.9%	56.7%	66.7%	85.7%	93.8%	81.1%	83.9%	79.1%	83.0%	76.2%	81.3%	79.2%	86.9%
Requiring rescue medication (CSRTable 35)	26.4%	9.8%	30.4%	10.3%	6.6%	1.8%	11.3%	6.3%	9.5%	3.6%	12.4%	5.4%	8.9%	1.9%
Vomiting or retching (CSR Table 36)	38.5%	31.3%	41.2%	32.4%	12.5%	4.5%	15.2%	16.1%	19.1%	16.1%	21.9%	17.0%	20.8%	13.1%
More than mild nausea (CSR Table 37)	21.4%	16.2%	25.0%	17.0%	7.8%	3.6%	10.6%	3.6%	11.5%	11.6%	8.7%	8.0%	9.0%	6.5%

The CHMP acknowledged that these data represent somewhat comparable trends in distribution.

Ancillary analyses

Heterogeneity

The CHMP raised questions regarding the design of the pivotal study mainly due to a wide ***variety of*** chemotherapy regimens administered, likely regional differences in patient care and concerns that the randomisation and the statistical analysis does not consider the influence of emetogenicity potential of primary diseases possibly confounding the complete control positives or negatives giving rise to concerns about the comparability of treatment groups and the assay sensitivity of the study.

In response the applicant emphasized that the concept of this development were the comparison of two routes of delivery of granisetron in which the only difference expected between these routes was PK. To address the issue of wide variety of chemotherapy regimens the applicant argued that the treatment regimens used in Study 392MD/15/C were examined by an expert independent oncologist and grouped into 28 categories with similar emetogenic chemotherapies (MEC or HEC) which where balance in both treatment arms. According to the applicant these groupings are expected to reduce the perceived heterogeneity among the treatment regimens. Furthermore the most important variables of treatment are the inclusion or exclusion of cisplatin and the classifying of the treatment as moderately or highly emetogenic.

In Study 392MD/15/C, 69.9% of patients received a cisplatin-based regimen. Cisplatin is the most frequently used chemotherapeutic agent in multiple day chemotherapy. The Applicant provided further analysis of the balance of chemotherapy regimens administered between treatment groups in Study 392MD/15/C in Table 9. and noted that the data confirm that cisplatin use by day was also balanced between the treatment groups.

Table 9: Patients Receiving Cisplatin: ITT Population, Split by Duration

ITT		TDS	Oral	Total
All	N	318	323	641
	Cisplatin	221 (69.5%)	227 (70.3%)	448 (69.9%)
3-day	N	205	210	415
	Cisplatin	149 (72.7%)	150 (71.4%)	299 (72.0%)
4-day	N	17	18	35
	Cisplatin	11 (64.7%)	15 (83.3%)	26 (74.3%)
5-day	N	81	83	164
	Cisplatin	58 (71.6%)	59 (71.1%)	117 (71.3%)

KEY: TDS=transdermal delivery system; ITT=Intention-to-treat

The applicant performed a logistic regression analysis for effect modification in the pivotal Study 392MD/15/C. ***Table 10*** below summarizes the results of the logistic regression analysis taking into account five selected factors (regimen (cisplatin present/absent); emetogenicity of regimen (MEC or HEC); Country, Region, emetogenic potential of primary disease).

In all five cases the P value for the interaction did not achieve statistical significance (P > 0.05). Therefore the applicant concluded that the treatment effect is similar, except for random fluctuations across the subgroups.

Table 10: Analysis of Complete Control in the FAS Stratified by Country, Region, Cisplatin and Emetogenic Potential of Primary Disease

FAS	TDS		Oral		Factor	P*
	n	CC	n	CC		
Regimen						
Cisplatin	220	120 (54.6%)	226	135 (59.7%)	Treatment x regimen	0.689
No cisplatin	88	65 (73.9%)	87	70 (80.5%)		
Emetogenicity of Regimen						
MEC (Hesketh 3-4)	72	55 (76.4%)	93	73 (78.5%)	Treatment x emetogenicity CT	0.848
HEC (Hesketh 5)	236	130 (55.1%)	220	132 (60.0%)		
Country						
Bulgaria + Serbia	63	34 (54.0%)	70	37 (52.9%)	Treatment x country	0.583
Poland + Czech Rep	20	12 (60.0%)	24	18 (75.0%)		
Romania	86	57 (66.3%)	82	62 (75.6%)		
Russia	34	26 (76.5%)	51	35 (68.6%)		
India	44	24 (54.5%)	32	20 (62.5%)		
US	33	21 (63.6%)	24	20 (83.3%)		
Mexico	28	11 (39.3%)	30	13 (43.3%)		
Region						
Eastern Europe	169	103 (60.9%)	176	117 (66.5%)	Treatment x	0.532
Russia	34	26 (76.5%)	51	35 (68.6%)	region	
India	44	24 (54.5%)	32	20 (62.5%)		
US	33	21 (63.6%)	24	20 (83.3%)		
Mexico	28	11 (39.3%)	30	13 (43.3%)		
Emetogenic Potential of Primary Disease**						
Yes	95	48 (50.5%)	87	45 (51.7%)	Treatment x	0.491
No	213	137 (64.3%)	226	160 (70.8%)	emetogenic	
					potential of primary disease	

KEY: CC=complete control; CT=chemotherapy; FAS=Full analysis set; HEC=highly emetogenic chemotherapy; MEC=moderately emetogenic chemotherapy; TDS=transdermal delivery system; US=United States

* Logistic regression including terms for Treatment, Non-rescue anti-emetics during the primary endpoint evaluation period (PEEP) and interaction

** Primary disease site assumed to have emetogenic potential: gynaecological, gastrointestinal

Further to these analyses, the applicant provided several arguments related to other clinical studies for the development of anti-emetics for CINV, the standardize management of monitoring in study 392MD/15/C, as well as the evaluation of assay sensitivity of the study.

The CHMP agreed that primary disease is not an important factor in emetogenicity, provided the primary site is outside the CNS; only primary brain tumor or brain metastases can have an impact on nausea and vomiting. The CHMP acknowledged that at baseline patients in the studies of other anti-emetics had a broad range of primary disease with varying emetogenic potential; thus study 392MD/15/C was conducted in line with this approach and precedent. Investigators launching a clinical trial intended to assess the efficacy of an antiemetic drug are free to choose among all the available regimens a few regimes within the same emetogenicity class (HEC or MEC). However CHMP emphasized that the use of a wide range of regimes in the same trial as much as different primary diseases and regional differences in patient care can make the comparability of treatment groups difficult and may compromise the assay sensitivity of studies. However it is acknowledged that in this case the pivotal trial shows non inferiority versus the 2mg oral dosage for the overall population providing valuable information close to a real live scenario making the study sufficiently informative for a new mode of administration in a substance with established benefit risk profile.

Clinical relevance of inferior plasma levels

During the procedure the applicant was requested to provide argumentation that the difference in plasma levels between granisetron oral and granisetron patch is not clinically relevant concerning efficacy overall and specially during the first day of chemotherapy.

The applicant used a logistic regression to test for an association between each PK parameter and achieving CC on Day 1.

Methodologically the logistic regression model assumed a linear relationship between the log odds of achieving CC and log transformed PK parameters, i.e. a sigmoidal relationship between the probability of achieving CC and log transformed PK parameters. This analysis included PK parameter, treatment group, Day 1 emetogenicity, chemotherapy naïve, gender, age and all interactions. In each case, the PK parameter was included in the model and the remaining were added, if significant ($P < 0.05$), in a stepwise fashion. The final models for each of the PK parameters are presented in **Table 1**, **Table 2** and **Table 3** below.

For both AUC and Cmax no statistically significant association with CC was observed, suggesting that within the range covering both granisetron TDS and oral granisetron at 2 mg QD, CC on the first day of chemotherapy is not dependent on daily granisetron exposure or achieved maximum levels. The relationship between observed plasma concentration and % CC on Day 1 was statistically significant ($P = 0.0038$).

Table 1: Logistic Regression Results – Relationship Between CC (Day 1) and log_{10}AUC, Including Adjustment for Significant Background Factors

Model Parameter	Parameter Estimate	P-value
Intercept	-1.1166	0.1586
Log_{10}(AUC)	0.4479	0.1607
Age	0.0364	0.0001

KEY: AUC=area under the plasma concentration-time curve

Table 2: Logistic Regression Results – Relationship Between CC (Day 1) and $log_{10}C_{max}$, Including Adjustment for Significant Background Factors

Model Parameter	Parameter Estimate	P-value
Intercept	-0.6652	0.2150
$Log_{10}(C_{max})$	0.5451	0.0518
Age	0.0366	<0.0001

KEY: C_{max}=maximum plasma drug concentration

Table 3: Logistic Regression Results – Relationship Between CC (Day 1) and log_{10}Plasma Concentration, Including Adjustment for Significant Background Factors

Model Parameter	Parameter Estimate	P-value
Intercept	2.4164	0.1340
Log_{10}(plasma concentration)	0.4607	0.0038
Day 1 emetogenicity	-0.5814	0.0499
Age	0.0347	0.0003

The geometric mean plasma level was 2.2-fold higher for oral granisetron compared to granisetron

TDS. ***Figure 1*** (log scale) and ***Figure 2*** (linear scale) shows the modelled probability of achieving CC on Day 1, and its 95% confidence interval (CI). *Figure 1* and shows that based on the obtained statistically significant association, the change in the probability of achieving CC on D1 across the range of observed granisetron plasma levels at the start of chemotherapy for oral granisetron and granisetron TDS is shallow. Figure 1 also shows the observed D1 CC figures (82.0% for granisetron TDS and 88.5% for oral granisetron). This demonstrates that a 14-fold increase in granisetron levels would be required to increase the probability of achieving CC from 82 to 88.5%, which is much higher than the observed 2.2-fold difference in geometric mean granisetron plasma levels for oral granisetron and granisetron TDS.

Figure 1: Modelled Relationship (& 95% CIs) Between CC (Day 1) and Plasma Concentration, After Adjustment for Background Factors

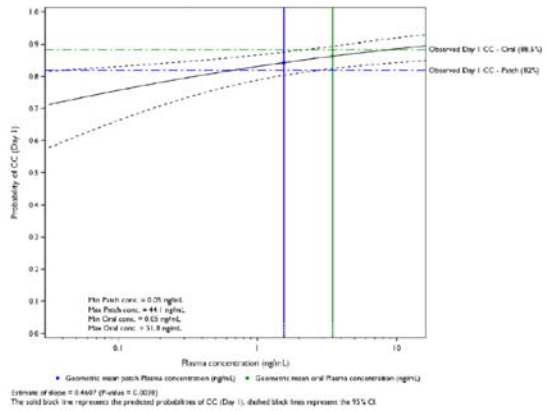
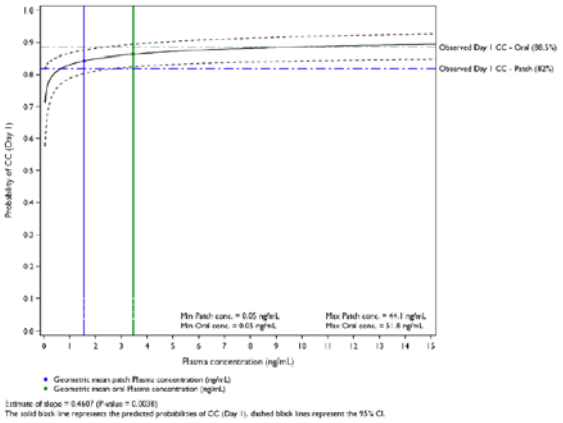


Figure 2: Modelled Relationship (& 95% CIs) Between CC (Day 1) and Plasma Concentration, After Adjustment for Background Factors



The applicant provided also predicted probabilities of achieving CC for treatment groups, based on granisetron ***geometric mean*** levels (see **Table 4**) for the two treatment groups, based on the modeled relationship and noted that based on this relationship the observed difference in geometric

mean plasma levels for oral granisetron and granisetron TDS would lead to only a minimal difference in the probability of achieving CC (84.4% for granisetron TDS and 86.4% for oral granisetron), with the 95% CIs almost completely overlapping.

Table 4: Estimates of Modelled CC (Day 1) Probabilities for Each Treatment Group Separately, Based on Geometric Mean Granisetron Levels

	TDS		Oral	
PK Parameter	**Geometric Mean Value**	**Probability of CC (Day 1) (95% CI)**	**Geometric Mean Value**	**Probability of CC (Day 1) (95% CI)**
Plasma concentration (ng/mL)	1.55	0.844 (0.804, 0.877)	3.45	0.864 (0.825, 0.895)

KEY: CC=complete control; CI=confidence interval; PK=pharmacokinetic; TDS=transdermal delivery system

Furthermore the applicant noted that the observed plasma levels in the granisetron oral and TDS groups at Visit 1 differ by a factor of 2.2 in geometric mean. An oral 1 mg twice daily (BID) dosing regimen is approved for CINV and therefore by implication is considered equally as effective as 2 mg QD. The plasma level one hour after the first dose (i.e. the start of chemotherapy) dosing for the 2 mg QD regimen would be expected to be 2-fold that for the oral 1 mg BID dosing regimen. Thus, a difference in plasma level of the order of approximately 2-fold, as observed when comparing oral granisetron to granisetron TDS, should be acceptable. It is also noteworthy that in both treatment groups the granisetron level at the start of chemotherapy was below LLOQ (0.05) in a number of subjects. This number was more than twice as high in the oral granisetron group compared to the granisetron TDS group: 26/235 (11.1%) vs 12/230 (5.2%) respectively.

Besides overall CC, oral granisetron and granisetron TDS were also compared based on CC on each individual day. The results of this analysis are presented in ***Table 6*** below. The criterion for non-inferiority was met for each individual day of treatment, as the lower limit of the 95% CIs were above the non-inferiority margin of -15%. The applicant noted that for granisetron TDS the % CC on each day was relatively constant. For oral granisetron a marked drop in % CC was observed on Days 2-5 relative to Day 1. This observation was also confirmed statistically, comparing CC on Days 1 and 2 for both oral granisetron and granisetron TDS using McNemar's test (Oral: P <0.001; TDS: P = 0.212).

The applicant noted that in view of this observation, the possible relevance of differences in granisetron plasma levels in terms of clinical efficacy may be questioned, as the observed drop in % CC after Day 1 for oral granisetron cannot be explained by changes in granisetron plasma concentrations or exposure.

For oral granisetron, exposure even increases slightly during continued use due to accumulation to steady-state levels (see Study 392MD/11/C where oral graniseteron is taken for 5 days). Granisetron TDS is designed to deliver relatively constant granisetron levels for multiple days (as confirmed in the performed clinical pharmacology studies) and therefore plasma levels will be relatively similar on the first and second day of chemotherapy. The applicant argued that therefore on the second day of chemotherapy the difference in granisetron plasma levels for oral granisetron and granisetron TDS can be considered to be at least similar to Day 1. However on Day 2 only a marginal difference in % CC was observed. This might highlight the lack of a clear dependency of CC on granisetron levels, when comparing granisetron TDS and oral granisetron at 2 mg QD.

Table 6: Complete Control on Each Individual Day (Study 392MD/15/C)

Day	TDS CC	Oral CC	Difference in CC%	
	n (%)	n (%)		[95% CI]
1	250 (82.0%)	277 (88.5%)	-6.53	[-12.11, -0.95]
2	240 (78.7%)	252 (80.8%)	-2.08	[-8.42, 4.26]
3	223 (73.6%)	230 (73.7%)	-0.12	[-7.08, 6.84]
4	218 (78.1%)	222 (78.7%)	-0.59	[-7.39, 6.22]
5	219 (83.0%)	231 (85.6%)	-2.60	[-8.78, 3.58]

KEY: CC=complete control; CI=confidence interval; TDS=transdermal delivery system; n=number of patients

The CHMP acknowledged that the gradual increase in plasma levels of granisetron following application of the transdermal patch and possible slower onset of efficacy compared to 2 mg oral granisetron at the start of chemotherapy can be managed with clear instructions in the SmPC that the TDS should be applied 24-48 hours before chemotherapy.

The slower onset of efficacy can be balanced restricting the indication to patients having swallowing difficulties where the benefits of a transdermal system are obvious.

Additional Efficacy Analyses

The generalisation of the primary endpoint results was examined using a breakdown by the categories: gender, (actual) cisplatin and corticosteroid use, planned duration of chemotherapy regimen and chemotherapy naivety, and is summarised in Table 33 and Figure 13

Table 33: Study 392MD/15/C Complete Control by Strata (PPS, Study 15/C)

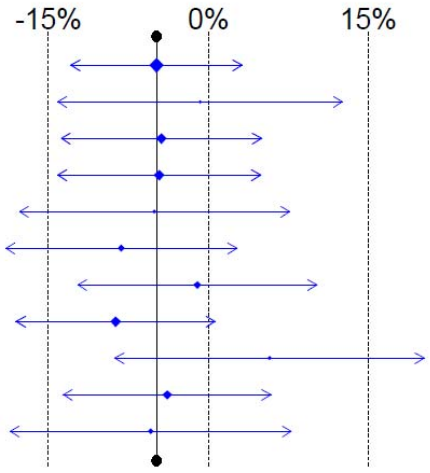
		Granisetron TDS		Oral Granisetron		Difference (%)[a]	
	CC	N	%	n	%	Estimate	95% CI
Gender							
Male	N	137		145			
	Yes	88	64.2	105	72.4	-8.18	-19.01, 2.65
	No	49	35.8	40	27.6		
Female	N	147		153			
	Yes	83	56.5	88	57.5	-1.05	-12.26, 10.15
	No	64	43.5	65	42.5		
Actual cisplatin and CS use							
Cisplatin	N	203		215			
	Yes	111	54.7	127	59.1	-4.39	-13.88, 5.10
	No	92	45.3	88	40.9		
Non-cisplatin + CS	N	52		56			
	Yes	38	73.1	47	83.9	-10.85	-26.28, 4.57
	No	14	26.9	9	16.1		
Non-cisplatin – CS	N	29		27			
	Yes	22	75.9	19	70.4	5.49	-17.73, 28.71
	No	7	24.1	8	29.6		
Planned duration of chemotherapy							
3 days	N	183		190			
	Yes	110	60.1	124	65.3	-5.15	-14.96, 4.65

	No	73	39.9	66	34.7		
4/5 days	N	101		108			
	Yes	61	60.4	69	63.9	-3.49	-16.65, 9.66
	No	40	39.6	39	36.1		
Chemotherapy naivety							
Naïve	N	83		81	N		
	Yes	114	56.7	142	65.4	-8.72	-18.05, 0.60
	No	87	43.3	75	34.6		
Non-naïve	N	201		217			
	Yes	57	68.7	51	63.0	5.71	-8.79, 20.21
	No	26	31.3	30	37.0		

Source: Study 392MD/15/C; a: Estimated via normal approximation to the binomial; CC=complete control, CI: confidence interval, CS: corticosteroid; N=Number of randomised patients in the respective treatment group; n=Number of patients; %=Percentage based on N

Figure 13: Subgroups: Best Estimates of Difference and 95% Confidence Intervals (CC) (PPS, Study 15/C); C/S: Corticosteroids

Subgroup	n	Estimate	95% CI
Overall	582	-4.89	-12.91, 3.13
MEC	156	-0.80	-14.16, 12.55
HEC	426	-4.43	-13.82, 4.95
Cisplatin	415	-4.65	-14.18, 4.88
No Cisplatin	167	-5.06	-17.76, 7.64
Male	282	-8.18	-19.01, 2.65
Female	300	-1.05	-12.26, 10.15
Chemo-naive	418	-8.72	-18.05, 0.60
Non-naive	164	5.71	-8.79, 20.21
C/S	366	-3.88	-13.61, 5.84
No C/S	216	-5.43	-18.62, 7.76



Gender differences. Study 15/C revealed tendency for better efficacy of granisetron TDS in females vs. males. According to the applicant, the reason for having lower bound of the 95% CI below -15% in males as compared to females is due to underpowered study for this analysis. In addition, the efficacy results do not correlate with exposure differences between males and females.

Corticosteroid Use. The CC proportions divided by CS use and by emetogenicity or cisplatin use were assessed and study results revealed comparable point estimates. CSs had an additive effect on CC during PEEP, although without significant interaction during a logistic regression analysis. The effect was observed in both study arms, numerically more in Oral vs TDS groups, 7.2% vs 5.1%, respectively.

Summary of the main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial

Title: A randomised, active control, double-blind, double-dummy, parallel-group, multi-national study to assess the efficacy, tolerability and safety of the granisetron transdermal delivery system (GTDS) in chemotherapy-induced nausea and vomiting (CINV) associated with the administration of moderately or highly emetogenic multi-day chemotherapy.			
Study identifier	392MD/15/C		
Design	multi-centre, randomised, active control, double-blind, double-dummy, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		treatment period of 7 days and a follow-up period of 14 days. screening period of 4 to 12 days not applicable
Hypothesis	Non-inferiority: This study was designed to establish whether the GTDS was non-inferior to oral granisetron in the prevention of CINV associated with ME or HE multi-day chemotherapy. The primary efficacy endpoint was the percent of patients achieving CC from the first administration until 24 h after the start of the last day's administration of the multi-day ME or HE chemotherapy regimen.		
Treatments groups	Patch group		Treatment duration: 7 days, Number randomized and received study treatment (GTDS) and had at least one efficacy assessment after the start of chemotherapy: 308
	Oral group		Treatment duration: equal to number of days of ME or HE chemotherapy, Number randomized and received study treatment (capsule) and had at least one efficacy assessment after the start of chemotherapy: 313
Endpoints and definitions	Primary endpoint	Efficacy	% of patients achieving complete control (CC) of CINV from the first administration until 24 h after the last administration of cytotoxic regimen with moderate emetogenicity (ME) or high emetogenicity (HE) potential (according to Hesketh Classification) The primary endpoint of the trial was the composite endpoint complete control (CC) of CINV over the whole period at risk from the first dose of chemotherapy to 24 hours after the last dose of chemotherapy (3, 4 or 5 days). CC was defined in study 15/C as no vomiting and/or retching, no more than mild nausea and no rescue medication.

	Secondary and other:	Efficacy, safety and other (PK)	**Efficacy evaluation (secondary):** • CC of CINV during successive 24 hour intervals from the first administration until 24 h after the last administration of the cytotoxic agents(s) with ME or HE potential. • In the subgroups of patients receiving 3 day and 4 day regimens, comparison of the TDS with oral granisetron with respect to CC in the period between 24 hours after the last administration of the ME or HE multi-day chemotherapy and patch removal. **Safety:** • Adverse Events collected from signed informed consent until 14 days after patch removal (defined as AEs) • Treatment Emergent AEs (TEAEs) from time of first oral capsule until 14 days after patch removal • Clinically relevant changes in vital signs, ECG and laboratory parameters from Screening to End of Treatment **Other:** • % of patients with adequate patch adhesion during the patch application period • Granisetron plasma concentration and metabolite profile at Visit 1 (1 h (+/-10 min) post capsule ingestion) and at Visit 6.
Database lock	The database was closed on 09 November 2006 and data were unblinded on 10 November 2006. The database was re-opened on 26 February 2007 to correct an error in adverse event coding. It was re-locked on 02 March 2007.		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	The Per Protocol Set (PPS) and Full Analysis Set (FAS) analyses: PPS was defined as all FAST patients without violations of the protocol which directly impinged on or affected the primary endpoint FAS was defined as a number randomized and received study treatment and had at least one efficacy assessment after the start of chemotherapy; Time points: GTDS: treatment period of 7 days; oral group: equal to number of days of ME or HE chemotherapy.

Descriptive statistics and estimate variability	Treatment group	**Granisetron TDS** n %	**Oral Granisetron** n %	**Adjusted Logistic Regression[a]** Difference (%) Estimate
	Number of subjects	**(N = 284)**	**(N = 298)**	
	PPS: Complete Control Yes No	 171 60.2 113 39.8	 193 64.8 105 35.2	-4.89
	Number of subjects	**(N = 308)**	**(N = 313)**	
	FAS: Complete Control Yes No	 185 60.1 123 39.9	 205 65.5 108 34.5	-5.77

Effect estimate per comparison	Composite Primary endpoint	Comparison groups	Granisetron TDS vs oral
		Difference (%) as assessed via adjusted Logistic Regression[a] analysis	PPS: -4.89 FAS: - 5.77
		Non-Inferiority as per 95%CI[b]	PPS: -12.91, 3.13 FAS: -13.51, 1.97
		P-value	NA
Notes	a: Primary comparison estimated via a logistic regression model, adjusting for treatment, gender, planned cisplatin and corticosteroid use, planned regimen duration and chemotherapy naivety as recorded in IVRS.; CI=confidence interval; N=Number of randomised patients in the respective treatment group; n=Number of patients; %=Percentage based on N b: The null hypothesis was that the GTDS is inferior to oral granisetron. The alternative hypothesis was that the GTDS is not inferior to oral granisetron. The hypothesis of non-inferiority was tested via a point estimate of the difference (D) in percentage CC between the two treatment groups, plus a 2-sided 95% confidence interval (CI). If the lower limit of this confidence limit was greater than -15%, the null hypothesis was rejected		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

Study 392MD/8/C. This exploratory Phase 2 efficacy study was initially conducted to investigate the efficacy of the granisetron TDS in *delayed CINV*. It was a randomised, active-control, double-blind, double-dummy, multi-centre Phase 2 study comparing the efficacy, safety and tolerability of a

granisetron TDS with oral granisetron in CINV following a single day administration of MEC. The trial was conducted at 21 sites in Germany.

The trial was constructed to allow study of both pre and post 24-hour phases of CINV following chemotherapy. The primary analysis was on TC of CINV for the period 24 to 120 hours following chemotherapy administration (i.e. delayed CINV). Total control (TC) was defined as no nausea, no vomiting, no use of rescue medication and no withdrawal from the study.

Inclusion criteria: (i) ECOG status < 2; (ii) Life expectancy of at least 3 months; (iii) Chemotherapy-naïve for at least 6 months since last chemotherapy; (iv) At least 3 weeks since last major surgery, including thoracotomy, laparotomy, craniotomy or vascular surgery involving the major vessels; (v) Scheduled to receive a single-day regimen of moderately emetogenic chemotherapy (i.e. any dose of carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, mitoxantrone; methotrexate (>250 mg/m2), cyclophosphamide (<1500 mg/m2), doxorubicin (>25 mg/m2) or cisplatin (<50 mg/m2) infused over 1-4 hours.

Exclusion criteria: (i) Tumours of the head, neck or stomach; (ii) Received radiation therapy involving the abdomen or pelvis within the 48 hours period prior to, or were scheduled to receive such radiation, during the treatment period.

Unlike Study 15/C, the exploratory 8/C study was designed without CS use.

The primary efficacy endpoint was the proportion of patients achieving TC of CINV for the period 24 to 120 hours following chemotherapy administration (i.e. delayed CINV). This was a *superiority study for delayed CINV:* based on a logistic regression model (with treatment, centre, gender and use of nicotine as factors), the 2-sided hypothesis that the granisetron TDS is not different to the single oral dose of granisetron (2 mg) was tested with an α level of 0.0499 on data from the intention-to-treat (ITT) population.

Secondary endpoints were: (i) proportion of patients achieving TC of CINV during the 0-24 hour time period post chemotherapy; (ii) proportion of patients achieving TC of CINV during the 0-120 hour time period post chemotherapy.

Oral active and oral placebo were taken 1 hour before the administration of ME chemotherapy. Patches were applied 24 hours before chemotherapy and remained in-situ for 4 days after chemotherapy – 5 days in total.

Originally a total of 210 patients were planned to be randomised. However, an interim analysis of the results all patients enrolled until 31 March 2005 (133 patients) suggested that although the granisetron TDS showed comparable efficacy to oral granisetron for the first 24 hours, there was no evidence of superiority during the period 24 - 120 hours post chemotherapy. Therefore, patient recruitment was halted at the end of April 2005, at which time 179 patients had been randomised.

2.5.3. Discussion on clinical efficacy

The efficacy of granisetron TDS has been studied in ten clinical studies involving 1,386 subjects (576 healthy subjects and 810 cancer patients with CINV), of whom approximately 58 % were the target patient population - cancer patients undergoing chemotherapy. The clinical development strategy was designed to bridge to the previous findings of efficacy and safety for the reference product. The performed study program as well as the size of the database is considered adequate for this hybrid application.

During the procedure the design of the pivotal study was challenged mainly due to a wide ***variety of chemotherapy regimens*** administered, likely ***regional differences*** in patient care and concerns that the randomisation and the statistical analysis not considering the influence of emetogenicity potential of ***primary diseases*** possibly confounding the complete control positives or negatives giving rise to concerns about the comparability of treatment groups and the assay sensitivity of the study.

The applicant argued that the development of granisetron was not based on NME but on new route of administration and could show that from 28 categories with similar emetogenic chemotherapies, the most important variables – the fact of cisplatin administration and the emetogencity (MEC or HEC) were balanced between the study arms.

Using logistic regression analysis for effect modification in the pivotal Study taking account the five most relevant selected factors (regimen (cisplatin present/absent); emetogenicity of regimen (MEC or HEC); Country, Region and emetogenic potential of two essential primary diseases (gynecology and GI) the applicant could show that the P value for the interaction did not achieve statistical significance ($P > 0.05$).

Regional differences in patient care were addressed through standardized management without any findings indicating regional differences in care.

The challenging of the assay sensitivity of the pivotal study was addressed by conducting several sensitivity analyses to confirm non-inferiority, in particular, examining subgroups of patients who received cisplatin-containing regimens and showing consistent results. The CHMP acknowledged that in this case the pivotal trial shows non inferiority versus the 2mg tablet for the overall population providing valuable information close to a real live scenario and making the study sufficiently informative for a new mode of administration in a substance with established benefit risk profile.

The applicant provided relevant arguments why the difference in plasma levels between granisetron oral and granisetron TDS should not be clinically relevant concerning efficacy overall and specially during the first day of chemotherapy arguing that the observed statistically significant difference of 2.2 times in mean plasma levels on D1 is close to the difference observed in another approved posology for oral granisetron (1mg BID vs 2 mg QD), that the probabilities to achieve CC on D1 for TDS and oral formulation are quite close each to other (0.844 vs 0.864, respectively) and that there are inconsistencies in changes in plasma concentrations as compared to changes in respective CC proportions highlighting the lack of a clear dependency of CC on granisetron levels.

The CHMP acknowledged that the gradual increase in plasma levels of granisetron following application of the transdermal patch and possible slower onset of efficacy compared to 2 mg oral granisetron at the start of chemotherapy can be managed with clear instructions in the SmPC that the TDS should be applied 24-48 hours before chemotherapy.

The slower onset of efficacy can be balanced restricting the indication to patients having swallowing difficulties where the benefits of a transdermal system are obvious.

The CHMP recommended including QoL (Functional Living Index of Emesis (FLIE) questionnaire) as an assessment in the future clinical programme, including the ongoing paediatric studies.

2.5.4. Conclusions on the clinical efficacy

For this Hybrid application the applicant performed one clinical pivotal study to show non inferiority of the granisetron TDS to 2mg tablet. Concerns of heterogeneity in the design of the pivotal study and inferior plasma levels at day 1 leading to inferior efficacy at day 1 were adequately addressed by the applicant.

The pivotal trial shows non inferiority versus the 2mg oral formulation for the overall population providing valuable information close to a real live scenario and making the study sufficiently informative for a new mode of administration in a substance with established benefit risk profile.

The gradual increase in plasma levels of granisetron following application of the transdermal patch and possible slower onset of efficacy compared to 2 mg oral granisetron at the start of chemotherapy can be managed with clear instructions in the SmPC that the TDS should be applied 24-48 hours before chemotherapy.

The slower onset of efficacy can be balanced restricting the indication to patients having swallowing difficulties where the benefits of a transdermal system are obvious.

2.6. Clinical safety

Introduction

The safety of granisetron TDS is based on the clinical studies performed with this formulation and the available post-marketing safety data for this medicinal product. The main source for the integrated safety profile is based on two studies with cancer patients (8/C and 15/C); the integrated summary for healthy subjects is also presented. In addition, the safety profile of the reference product is taken into consideration.

Patient exposure

In the original studies 796 (392 healthy subjects, 404 cancer patients) were exposed to granisetron TDS. Across these studies, durations of exposure varied from 1 day to 23 days. The majority of healthy subjects wore the 52 cm² TDS for a minimum of 6 days (range 1-23 days) with 202 healthy subjects exposed to granisetron TDS for 23 days. All the cancer patients were exposed to the 52 cm² TDS, the majority for 5, 6, or 7 days with 246 cancer patients treated for 7 days.

The mean age of the cancer group was 55 years and the healthy population was 37 years. The overall age range in studies was 16 – 86 years and the populations were predominantly of Caucasian ethnicity.

In addition, post-marketing safety data covering a 21 months period of use in the US (12 September 2008 through 11 June 2010) was also provided.

Adverse events

In the main study the most commonly reported adverse reaction was constipation, occurring in approximately 10.4% of patients. The majority of adverse reactions were mild or moderate in severity.

Table 27 Treatment Emergent Adverse Events Occurring in >1% of Either Treatment Group

System Organ Class Preferred Term	TDS n (%) E (N=316)	Oral n (%) E (N=321)	Total n (%) E (N=637)
Gastrointestinal Disorders Constipation	33 (10.4%) 35	18 (5.6%) 18	51 (8.0%) 53
Gastrointestinal Disorders Diarrhoea	16 (5.1%) 16	17 (5.3%) 19	33 (5.2%) 35
Metabolism And Nutrition Disorders Anorexia	15 (4.7%) 16	17 (5.3%) 17	32 (5.0%) 33

System Organ Class Preferred Term	TDS n (%) E (N=316)	Oral n (%) E (N=321)	Total n (%) E (N=637)
Blood And Lymphatic System Disorders Neutropenia	10 (3.2%) 10	14 (4.4%) 14	24 (3.8%) 24
Nervous System Disorders Headache	8 (2.5%) 8	13 (4.0%) 15	21 (3.3%) 23
General Disorders And Administration Site Conditions Asthenia	11 (3.5%) 12	8 (2.5%) 8	19 (3.0%) 20
General Disorders And Administration Site Conditions Fatigue	7 (2.2%) 7	10 (3.1%) 10	17 (2.7%) 17
General Disorders And Administration Site Conditions Pyrexia	7 (2.2%) 9	9 (2.8%) 10	16 (2.5%) 19
Gastrointestinal Disorders Abdominal Pain	7 (2.2%) 8	8 (2.5%) 10	15 (2.4%) 18
Blood And Lymphatic System Disorders Anaemia	8 (2.5%) 8	6 (1.9%) 7	14 (2.2%) 15
Respiratory, Thoracic And Mediastinal Disorders Dyspnoea	9 (2.8%) 9	4 (1.2%) 4	13 (2.0%) 13
Blood And Lymphatic System Disorders Leukopenia	5 (1.6%) 5	8 (2.5%) 9	13 (2.0%) 14
Blood And Lymphatic System Disorders Thrombocytopenia	4 (1.3%) 4	8 (2.5%) 12	12 (1.9%) 16
Blood And Lymphatic System Disorders Febrile Neutropenia	6 (1.9%) 7	5 (1.6%) 6	11 (1.7%) 13
Vascular Disorders Hypertension	4 (1.3%) 4	6 (1.9%) 8	10 (1.6%) 12
Gastrointestinal Disorders Dyspepsia	4 (1.3%) 4	5 (1.6%) 5	9 (1.4%) 9
Respiratory, Thoracic And Mediastinal Disorders Hiccups	4 (1.3%) 4	3 (0.9%) 3	7 (1.1%) 7
Vascular Disorders Hypotension	3 (0.9%) 3	4 (1.2%) 5	7 (1.1%) 8
General Disorders And Administration Site Conditions Mucosal Inflammation	1 (0.3%) 1	6 (1.9%) 8	7 (1.1%) 9
General Disorders And Administration Site Conditions Oedema Peripheral	2 (0.6%) 2	5 (1.6%) 5	7 (1.1%) 7
Skin And Subcutaneous Tissue Disorders Rash	4 (1.3%) 4	3 (0.9%) 3	7 (1.1%) 7
Metabolism And Nutrition Disorders Hypokalaemia	0 (0.0%) 0	6 (1.9%) 7	6 (0.9%) 7

System Organ Class Preferred Term	TDS n (%) E (N=316)	Oral n (%) E (N=321)	Total n (%) E (N=637)
Gastrointestinal Disorders Nausea	4 (1.3%) 4	2 (0.6%) 2	6 (0.9%) 6
Metabolism And Nutrition Disorders Dehydration	4 (1.3%) 4	1 (0.3%) 1	5 (0.8%) 5
Infections And Infestations Urinary Tract Infection	4 (1.3%) 4	1 (0.3%) 1	5 (0.8%) 5
Investigations Electrocardiogram QT Corrected Interval Prolonged	0 (0.0%) 0	4 (1.2%) 4	4 (0.6%) 4

KEY: n=number of patients; %=percentage of patients; E=number of events; TDS=transdermal delivery system

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

During the assessment process the applicant acknowledged a potential underreporting of the adverse events headache, constipation, dizziness and asthenia/fatigue and argued that comparisons across trials are cofounded by study-specific differences such as schedules of chemotherapy and patient visits, dose and study design as well as possibly by the higher familiarity of physicians with granisetron-containing products compared to the initial trials. Therefore the MAH included in addition, adverse reactions reported for other formulations of granisetron as class effects into the SmPC.

Serious adverse event/deaths/other significant events

The application included reports of two serious adverse events (SAEs) that were observed in the *healthy subject* studies - a cerebrovascular accident in Study 26/C (considered by the investigator to be unrelated) and atrial fibrillation case in Study 40/C (considered possibly related).

Twenty-two granisetron TDS *patients* recorded 33 SAEs (5.45%) compared with twenty patients in the oral granisetron group who recorded 32 SAEs (4.9%). Four cancer patients reported related events - three patients in the oral granisetron group had QTc prolongation reported as an SAE and one subject in the granisetron TDS group had constipation.

Eighteen cancer patients died as a result of AEs during the clinical trials; ten of the patients were treated with granisetron TDS and eight received oral granisetron. None of the deaths was considered related to granisetron TDS.

Laboratory findings

Overall, there were no significant consistent patterns of alterations in biochemistry, haematology and urinalysis measurements for the *cancer population*. Changes in vital signs data were not considered significant.

Other significant events

Skin irritation and sensitisation

The evaluation of skin irritation and sensitisation was primarily based on an analysis of 201 healthy volunteers included in study 26/C.

Generally, in all studies healthy subject population 46 AEs were recorded for application site erythema of granisetron TDS, seven AEs for application site pruritus, four AEs for application site irritation, four

AEs for application site reaction, two AEs for application site papules, one for application site dryness, one for application site eczema and one for application site pain.

Dermal tolerance in cancer patients was formally assessed in study 8/C. In addition, skin tolerance data were collected as AEs in study 15/C. In the cancer patient safety population three AEs were recorded for application site pruritis with one case of oedema. Of these, one case of pruritis and the oedema case were reported as related to study medication.

All cases were reported as of mild severity and none led to withdrawal from the studies.

The results of the dermal tolerance studies in both patients and healthy subjects suggest that mild irritant and hypersensitivity reactions are possible with granisetron TDS. As a consequence of this the precaution has been included in the EU SmPC Section 4.4.

Phototoxicity

Granisetron TDS did not show any potential for photoirritation or photosensitivity when tested in vivo in guinea-pigs. Granisetron was not phototoxic when tested in vitro in a mouse fibroblast cell line. When tested for potential photogenotoxicity in vitro in a Chinese hamster ovary (CHO) cell line, granisetron increased the percentage of cells with chromosome damage following photoirradiation.

Although, the clinical relevance of this finding is not completely clear, it was recommended to advise patients to avoid exposure to sunlight in section 4.4 and to mention the finding in 5.3 of the SmPC

Possible hypersensitivity/local tolerance

Hypersensitivity-type adverse events were reported in a total of 65/784 (8.3%) subjects treated with granisetron TDS in the clinical programme, including application site erythema (46 [5.9%]); application site pruritus (10 [1.3%]); application site irritation (4 [0.5%]); application site reaction (4 [0.5%]) and hypersensitivity (1 [0.1%]). With the exception of the case of hypersensitivity and two cases of application site pruritus, all hypersensitivity type adverse events were considered by the Investigator to be related to study treatment.

In addition, as of 11 June 2011, 13 adverse event reports of hypersensitivity reactions were received in the global safety database since launch, including application site erythema (3); application site rash (3); application site reaction (3); application site irritation (2); and application site pruritus (2). There were no SAE reports of hypersensitivity in the clinical trials for granisetron TDS, and all 13 post marketing cases of hypersensitivity type reactions reported were non-serious.

The CHMP considered that although reports of hypersensitivity reactions in the global safety database are rare, the possibility of such an event occurring cannot be ruled out. Hypersensitivity has therefore been added as a potential risk in the Risk Management Plan, including appropriate pharmacovigilance and risk minimization activities.

Safety in special populations

Special attention was given to subgroups of patients with impaired hepatic or renal function and no new information has been gathered during the course of the development programme for granisetron TDS with respect to this patient population. As no studies were performed in children no information is available for the paediatric population.

An analysis of age among granisetron TDS-treated patients was performed and no association with increased frequency of occurrence of AEs was found.

Safety related to drug-drug interactions and other interactions

No studies were performed on drug interactions with regard to safety.

Discontinuation due to adverse events

Adverse events were recorded as the reason for withdrawal in 24 subjects overall: 10 cancer patients from the granisetron TDS group, 7 cancer patients from the oral granisetron group and 6 healthy subjects from study 26/C and one healthy subject from 40/C.

In the healthy subject group, five of the withdrawals were considered related to study medication – (3 cases constipation, 1 case of atrial fibrillation and 1 case of abdominal pain) and one possibly related (atrial fibrillation). Three additional cases were unrelated, including an SAE of a cerebrovascular accident.

In cancer patients, most AEs leading to withdrawal were assessed as not related to study medication, but instead related to the underlying medical condition or the chemotherapy administered.

Post marketing experience

Granisetron TDS was first authorised on 12 September 2008. An Integrated Post-marketing Safety Report for granisetron TDS (patch 3.1 mg/24 hours) has been provided in support of the EU licensing application. This report covers the 21 month period from 12th September 2008 (IBD) to 11th June 2010. An estimated 80,940 patches have been distributed since launch through 11 June 2010. Based on the distributed patches of 80,940 units into the US market, the patient exposure has been estimated at 1,552 treatment years.

Overall, during this review period, the MAH has received 71 case reports: 34 from HCP, 36 from consumers and 1 from clinical trials. Seven reports were serious, two of those concerned cardiac disorders: sick sinus syndrome and atrial fibrilation. The MAH concluded that a review of all new safety information identified during this review period did not reveal any new safety signals.

Ongoing review of the reported detachment rate from the market gives no indication that this rate may be any higher than that reported in the Phase 3 clinical trial.

One unexplained case of *epilepsy* was observed postmarketing. The epileptogenicity is one of the observed effects in the acute non-clinical toxicity study. The applicant explained that the particular patient had a history of complex partial seizures and possible precipitating factors for TEAE. This is explanation was considered acceptable CHMP.

2.6.1. Discussion on clinical safety

The safety of granisetron TDS is based on a database generated in 796 healty subjects and cancer patients (392 and 404 cancer respectively). In addition to this, post marketing experience estimated at 1,552 treatment years and is contributing to the safety profiling. Thus, the size of the safety data base and the exposure over time could in principle be acceptable for an application for a new pharmaceutical form of a known active substance as it is the case with this application.

In the clinical studiers granisetron TDS, like other 5-HT3-antagonists, showed an increased risk of constipation, headache and hepatotoxicity. The post marketing experience did not reveal any new important risk identified and the safety concerns listed as potential risks are endorsed.

The CHMP noted a lower then historically expected reporting rate for oral granisetron 2mg in the clinical studies which was explained by the applicant by possible higher familiarity with the granisetron product compared to the initial trials and that comparisons across trials are confounded by study-specific differences such as schedules of chemotherapy and patient visits, dose and study design.

It was therefore considered adequate to add granisetron class effects seen with other formulations (oral and intravenous) in section 4.8 of the SmPC.

5-HT_3 receptor antagonists have been associated with QT interval prolongation. However, no clinically relevant effects on ECG have been observed in clinical studies with SANCUSO, including a thorough QT study in 240 healthy subjects.

Although no cases of phototoxicity were observed in man, findings in a laboratory model using Chinese Hamster Ovary (CHO) cells are suggestive of a potential photogenotoxic effect. As a consequence a warning regarding exposure to sunlight has been included in sections 4.4 and 5.3 of the SmPC.

Effects of photogenotoxicity observed in the pre-clinical tests and hypersensitivity reactions as observed in the safety database were added to the RMP as important potential risks and were reflected adequately in the relevant sections of the SmPC.

Taking into account the experience with the active substance in other formulations, the CHMP considers the safety profile of the patch acceptable.

The safety profile is reflected in section 4.8 of the SmPC.

2.6.2. Conclusions on the clinical safety

The clinical studies with granisetron TDS and the post marketing experience with the medicinal product did not reveal any new important risk. The known safety profile of granisetron has been taken into consideration and the CHMP concludes that the safety profile for Sancuso is acceptable. The SmPC adequately reflects this body of information.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 2. Summary of the risk management plan

Safety Concern	Agreed Pharmacovigilance Activities	Agreed Risk Minimisation Activities
Important Identified Risk:		
Complications of severe constipation	Routine pharmacovigilance, including cumulative assessment in the PSURs	*Routine risk minimisation:* SmPC Section 4.4 Special warnings and precautions for use states: *Gastrointestinal disorders: As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal*

	Heighten follow-up activities through structured questionnaire for spontaneous reports	*obstruction should be monitored following its administration.*
Important Potential Risks:		
QT Prolongation	Routine pharmacovigilance, including cumulative assessment in the PSURs	*Routine risk minimisation:* Section 4.4 Special warnings and precautions for use states: *Cardiac disorders: 5-HT_3 receptor antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities. This potentially may have clinical significance in patients with pre-existing arrhythmias or cardiac conduction disorders or patients who are being treated with antiarrhythmics or beta-blockers. No clinically relevant effects have been observed in clinical studies with SANCUSO.*
Photogenotoxicity	Routine pharmacovigilance, including cumulative assessment in the PSURs Heighten follow-up activities through structured questionnaire for spontaneous reports	*Routine risk minimisation:* SmPC Section 4.4 Special warnings and precautions for use states: *Exposure to sunlight: Granisetron may be affected by direct natural or artificial sunlight. Patients must be advised to cover the patch application site, e.g. with clothing, if there is a risk of exposure to sunlight throughout the period of wear and for 10 days following its removal.*

Hypersensitivity-type reactions	Routine pharmacovigilance, including cumulative assessment in the PSURs	<u>*Routine risk minimisation:*</u> Suitable statements in the EU SmPC: Section 4.3 Contraindications states that SANCUSO is contraindicated in patients with hypersensitivity to granisetron, other 5-HT_3 antagonists or any of the excipients of SANCUSO: *Hypersensitivity to the active substance (granisetron), to other 5-HT_3 receptor antagonists or to any of the excipients.* Section 4.4 Special warnings and precautions for use states: Application site reactions: In clinical trials with SANCUSO, application site reactions were reported which were generally mild in intensity and did not lead to discontinuation of use. If severe reactions, or a generalised skin reaction occur (e.g. allergic rash, including erythematous, macular, papular rash or pruritus), the transdermal patch must be removed. Section 4.8 Undesirable Effects lists hypersensitivity reactions (e.g. anaphylaxis and urticaria) as uncommon ADRs reported for other formulations of granisetron.
Off-label use	Routine pharmacovigilance, including cumulative assessment in the PSURs Additional activities Retrospective observational study of SANCUSO prescribing 2 years after launch User testing of the SANCUSO promotional materials 6 months after product launch in the first European market	<u>*Routine risk minimisation:*</u> Suitable statement in the EU SmPC: Section 4.1 Therapeutic indications specifies use of SANCUSO for: *SANCUSO transdermal patch is indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy, for a planned duration of 3 to 5 consecutive days, where oral anti-emetic administration is complicated by factors making swallowing difficult.*
Important Missing Information:		
Use in Pregnancy, Lactation	Routine pharmacovigilance, including cumulative assessment in the	<u>*Routine risk minimisation:*</u> SmPC Section 4.6 states: There are no data on the use of granisetron in

	PSURs	pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3). As a precautionary measure, it is preferable to avoid the use of SANCUSO during pregnancy.
Use in Pregnancy, Lactation *(Cont.)*		SmPC Section 4.6 states: It is unknown whether granisetron or its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with SANCUSO.
Use in paediatrics	Routine pharmacovigilance, including cumulative assessment in the PSURs	*Routine risk minimisation:* SmPC Section 4.2 Posology and method of administration states: *The safety and efficacy of SANCUSO in children aged 0 to 18 years have not yet been established.* SmPC Section 5.2, Pharmacokinetics, Paediatric Population states: No studies have been performed to investigate the pharmacokinetics of SANCUSO in paediatrics.
Safety and tolerability of SANCUSO in patients with clinically significant co-morbidities (e.g., hepatic, renal, cardiac, pulmonary disorders)	Routine pharmacovigilance, including cumulative assessment in the PSURs	*Routine risk minimisation:* SmPC Section 4.4: *Special populations:* *No special precautions are required for elderly patients and renally- or hepatically-impaired patients.* *Although no evidence of an increased incidence of adverse reactions have been observed in hepatically-impaired patients receiving granisetron orally and intravenously, based on granisetron pharmacokinetics, a degree of caution must be exercised in this population.* *Cardiac disorders:* *5-HT$_3$ receptor antagonists, such as granisetron, may be associated with arrhythmias or ECG abnormalities. This potentially may have clinical significance in patients with pre-existing arrhythmias or cardiac conduction disorders or patients who are being treated with antiarrhythmics or beta-blockers. No clinically relevant effects have been observed in clinical studies with SANCUSO.* *Renal or hepatic impairment* SmPC Section 5.2:

		No clinical studies have been performed specifically to investigate the pharmacokinetics of SANCUSO in patients with renal or hepatic impairment. No clear relationship between renal function (as measured by creatinine clearance) and granisetron clearance was identified in population PK modelling. In patients with renal failure or hepatic impairment, the pharmacokinetics of granisetron were determined following a single 40 μg/kg intravenous dose of granisetron hydrochloride.
Safety and tolerability of SANCUSO in patients with clinically significant co-morbidities (e.g., hepatic, renal, cardiac, pulmonary disorders) *(Cont.)*		*Hepatic impairment:* *In patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance was approximately halved compared to patients without hepatic impairment. Given the wide variability in pharmacokinetic parameters of granisetron and the good tolerance well above the recommended dose, dose adjustment in patients with functional hepatic impairment is not necessary.* *Renal impairment:* *No correlation between creatinine clearance and total clearance was observed in cancer patients, indicating no influence of renal impairment on the pharmacokinetics of granisetron*

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet does not meet all 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.* The applicant will address the outstanding minor issues concerning the user consultation before marketing the product.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Granisetron TDS delivers over 7 days an average of 3.1 mg of granisetron per day resulting in effective plasma concentrations 24-48h after application. Compared to the tablet granisetron TDS has the advantage of requiring only a single administration. It can be self applied by the patient at home and can be worn for up to 7 days, removing the need for repeated oral doses of granisetron. For Patients

with difficulties in swallowing the tablet is not a treatment option. These patients could benefit in an outpatient setting from granisetron TDS as they would otherwise have to attend a clinic or be admitted for daily i.v. CINV medication. Furthermore applying oral medications if at all possible is difficult and uncomfortable for these patients therefore the TDS formulation might might also have positive effects on treatment compliance.

Uncertainty in the knowledge about the beneficial effects.

There is no established relationship between granisetron plasma levels and control of CINV. However in the absence of measurements of concentrations at receptor level they are the best surrogate available to indicate that sufficient exposure to granisetron has been achieved to be of therapeutic benefit.

Non inferiority to the originator has been robustly demonstrated for the overall population an for all days of chemotherapy however the gradual increase in plasma levels of granisetron following application of the transdermal patch and the lower median plasma concentration with regards to the tablet at the first day of chemotherapy might be indicative for a slower onset of efficacy compared to 2 mg oral granisetron at the start of chemotherapy. Therefore reference was made in the indication to 5.1 of the SmPC where this relevant pharmacodynamic property is explained. Furthermore TDS is considered to be used in patients where the tablet is not a treatment option.

Risks

Unfavourable effects

Granisetron is a known active substance used for CINV; its general safety profile can be considered established. There are few new safety concerns regarding granisteron TDS compared to the tablet.

The results of the dermal tolerance studies in both patients and healthy subjects suggested that mild irritant and hypersensitivity reactions are possible with granisetron TDS. Reports of hypersensitivity reactions in the global safety database are rare but the possibility of such an event occurring cannot be ruled out. In addition to that findings in a laboratory model using Chinese Hamster Ovary (CHO) cells are suggestive of a potential photogenotoxic effect although no cases of phototoxicity were observed in man. These new safety issues with the TDS are acceptable and considered manageable as reflected in SmPC and RMP.

Uncertainty in the knowledge about the unfavourable effects

The safety profile of granisetron can be considered established. The clinical relevance of potential photogenotoxicity seen *in vitro* in a Chinese hamster ovary (CHO) cell line not completely clear and was not observed in non clinical in vivo studies or man. This finding is considered manageable as reflected in SmPC and RMP

Benefit-risk balance

Importance of favourable and unfavourable effects

Nausea and vomiting still remain a major issue for patients receiving chemotherapy. The distress resulting from these symptoms can escalate over time, and can potentially lead to a patient's refusal to continue with the most effective anti-tumour therapy. Complications can include dehydration and electrolyte imbalance, malnutrition or aspiration pneumonia and can be life-threatening. Failure to control these side effects can lead to 25% - 50% of patients delaying or refusing possible life saving

chemotherapy, or can result in increased demands and costs for the healthcare team if chemotherapy has to be rescheduled.

Patients with upper aerodigestive tumours following surgery or radiotherapy can have dry mouth, mucositis and/or difficulty in swallowing making oral medications difficult and uncomfortable, or impossible in some patients. The possible impact on treatment compliance is reasonable to expect.

Such patients, when in the outpatient setting, could benefit from granisetron TDS as they would otherwise have to attend a clinic or be admitted for daily i.v. CINV medication.

Therefore the need for new and more convenient administration of antiemetics used for multiday CINV is high and the favourable effects of an effective TDS reasonable to expect.

The safety profile of granisetron is well known and there are only few new safety concerns regarding granisteron TDS compared to the tablet such as hypersensitivity reactions and observations of photogenotoxicity in the non clinical model.

Benefit-risk balance

Discussion on the benefit-risk balance

Granisetron is licensed for the prevention of nausea and vomiting associated with emetogenic cancer therapy, including high-dose cisplatin, which has a strong emetic effect in more than 90 % of patients. Oral and i.v. formulations of granisetron have been available for over fifteen years. Granisetron has a well established safety profile and the safety concerns specific for the transdermal formulation can be adequately managed in clinical practice.

Nausea and vomiting still remain major issues for patients receiving chemotherapy. Failure to control these side effects can lead to delaying or refusing possible life saving chemotherapy. For patients with difficulties in swallowing the tablet is not a treatment option. These patients could benefit in an outpatient setting from granisetron TDS as they would otherwise have to attend a clinic or be admitted for daily i.v. CINV medication. Furthermore applying oral medications if at all possible is difficult and uncomfortable for these patients therefore TDS formulation might have also positive effects on treatment compliance.

In a pivotal, randomised, double-blind, Phase III efficacy study the applicant could show non-inferiority of granisetron TDS to 2 mg oral granisetron once daily in the prevention of nausea and vomiting in patients receiving multi-day chemotherapy for 3 to 5 consecutive days.

There is no established relationship between granisetron plasma levels and control of CINV and non inferiority against the originator has been shown for all days of treatment. However the gradual increase in plasma levels of granisetron TDS following application and the lower median plasma concentration shown in the pharmacokinetic studies with regards to the tablet at the first day of chemotherapy might be indicative for a slower onset of efficacy at the start of chemotherapy compared to 2 mg oral granisetron. Therefore reference was made in the indication to 5.1 of the SmPC where this relevant pharmacodynamic property is explained. Furthermore TDS is considered to be used in patients where the tablet is not a treatment option.

Considering the apparent benefit having this effective treatment of post chemotherapy nausea and vomiting also available for patients who have difficulties to swallow the CHMP consider the risk benefit balance for granisetron positive for the following indication:

SANCUSO transdermal patch is indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy, for a planned duration of 3 to 5

consecutive days, where oral anti-emetic administration is complicated by factors making swallowing difficult (see section 5.1).

4. Recommendations

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in 1.4 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent positions to the majority recommendation are appended to this report.