Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for naloxegol oxalate

Proprietary Product Name: Movantik

Sponsor: AstraZeneca Pty Ltd

June 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
API	active pharmaceutical ingredient
ASA	Australian Specific Annex
AUC	area under the plasma drug concentration-time curve
BBB	blood brain barrier
BLRSQ	Baseline Laxative Response Status Questionnaire
BM	bowel movement
BMI	body mass index
BSS	Bristol Stool Scale
BW	body weight
Cmax	maximum concentration of drug in serum
CNS	central nervous system
CSBM	complete spontaneous bowel movement
DILI	Drug Induced Liver Injury
DLP	Data Lock Point
EMA	European Medicines Agency
F_{Abs}	absolute bioavailability
FDA	Food and Drug Administration
IC50	half maximal inhibitory concentration
IV	intravenous
λz	elimination rate constant
LH	luteinising hormone
LIR	laxative inadequate responders
MEQ	morphine equivalent

Abbreviation	Meaning
MEU	morphine equivalent units
MRHD	maximum recommended human dose
MTP	multiple testing procedure
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OIC	opioid-induced constipation
P-gp	P-glycoprotein
PAC-QOL	Patient Assessment of Constipation Quality of Life Questionnaire
PAC-SYM	Patient Assessment of Constipation Symptom Questionnaire
PAMORA	peripherally acting μ-opioid receptor antagonist
PASS	post authorisation safety study
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
Ph Eur	European Pharmacopoeia
PI	Product Information
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PO	per os (oral)
PopPK	population pharmacokinetics
PRO	patient response outcomes
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
QoL	Quality of Life
SBM	spontaneous bowel movements
SmPC	Summary of Product Characteristics
$t_{½}$	elimination half-life

Abbreviation	Meaning
TEAE	treatment emergent adverse event
Tmax	time of maximum concentration of drug in serum
USP	United States Pharmacopoeia

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	5 January 2016
Date of entry onto ARTG	7 January 2016
Active ingredient:	Naloxegol oxalate
Product name:	Movantik
Sponsor's name and address:	AstraZeneca Pty Ltd 5 Alma Road North Ryde NSW 2113
Dose form:	Immediate release film coated tablets
Strengths:	12.5 mg, 25 mg
Containers:	OPA/Aluminium/PVC/Aluminium foil blisters
Pack sizes:	10 and 30 tablets blister packs
Approved therapeutic use:	Movantik is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).
Routes of administration:	Oral
Dosage:	The maximum recommended daily dose is 25 mg taken in the morning on an empty stomach.
ARTG numbers:	232030, 232029

Product background

This AusPAR describes the application by AstraZeneca Pty Ltd to register a new chemical entity, Movantik (active ingredient: naloxegol oxalate), as an oral agent for the treatment of opioid-induced constipation (OIC).

Naloxegol is a PEGylated derivative of the μ-opioid receptor antagonist naloxone. It does not cross the blood brain barrier. It is a peripherally acting μ-opioid receptor antagonist (PAMORA). The only other PAMORA approved in Australia is methylnaltrexone bromide (Relistor) which was approved in 2008 for treatment of OIC in patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient. Relistor is administered via subcutaneous injection.

Naloxegol has been proposed as an oral treatment for OIC. It has been approved in the EU and USA with more restrictive indications than have been proposed in Australia. In the EU, the indication is limited to OIC in adults with an inadequate response to laxative(s). In the USA the indication is limited to OIC in adults with chronic non-cancer pain. At the time of submission, it was under evaluation in Canada and Switzerland.

Oral naloxone, in combination with oxycodone (Targin) was approved in 2010 for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. Naloxone does cross the blood brain barrier but systemic effects are low due to a pronounced first pass effect and its very low oral bioavailability upon oral administration (<3%). Prucalopride (Resotrans) a selective, a 5HT4 agonist was approved in 2011 for the treatment of chronic functional constipation in adults in whom laxatives fail to provide adequate relief. Its indications stipulate that patients must have tried at least two different types of laxatives from different classes (at the highest tolerated recommended doses) for at least six months, but have not had adequate relief from constipation. Additionally, the indication for prucalopride stipulates that the benefit of continuing its use should be reconsidered if it is not effective within 4 weeks.

The European Medicines Agency (EMA) recently agreed on a new guideline for the clinical investigation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing.[1] That guideline will come into effect in the EMA in January 2016 and is under consideration for adoption by the TGA. That guideline has been included with the agenda papers. Advice relevant to this submission in that guideline includes: the importance of establishing the diagnosis of OIC; how to establish claims of laxative resistant OIC; whether the effect of the medicine varies with the dose of opioid taken by the patient or of the product; the importance of separately determining the effect of the medicine on patients with OIC due to use of opioids for cancer related pain; and the advisability of an active comparator trial to demonstrate non-inferiority. There is no current guideline adopted by the TGA for this condition.

Regulatory status

The international regulatory status at the time of submission is listed in Table 1.

[1] European Medicines Agency, "Guideline on the evaluation of medicinal products for the treatment of chronic constipation (EMA/CHMP/336243/2013)", 20 February 2014.

Table 1: International regulatory status of Movantik at time of submission.

Country	Submission date	Submission status	Approved indications
US	16 Sep 2013	Approved 16 Sep 2014	Movantik (naloxegol) is an opioid antagonist indicated for the treatment of OIC in adult patients with chronic noncancer pain
EU[a]	26 Aug 2013	Approved 8 Dec 2014	Moventig is indicated for the treatment of OIC in adult patients who have had an inadequate response to laxative(s)
Canada	28 Aug 2013	Approved 2 Jun 2015	Movantik (naloxegol oxalate) is indicated for the treatment of OIC in adult patients with non-cancer pain who have had an inadequate response to laxative(s)
Switzerland	1 Oct 2013	Approved 8 Jul 2015	Moventig is indicated for the treatment of adult patients 18 years and older with OIC with pain of non-malignant origin including patients with inadequate response to laxatives

a. Mutual Recognition Procedure - Centralised Procedure Rapporteur (Belgium) and Co-Rapporteur (Poland)

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

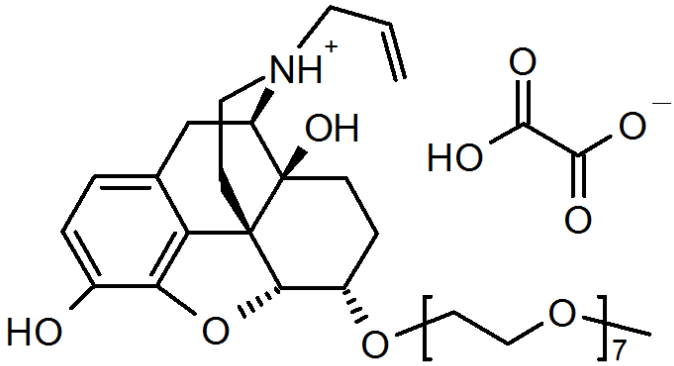
The peripherally acting μ-opioid receptor antagonist naloxegol oxalate, the oxalate salt of a PEGylated derivative of naloxone is developed for the treatment of OIC. The dossier states that in vitro studies demonstrate that naloxegol is a neutral antagonist of μ-opioid receptors, a neutral antagonist of δ-opioid receptors and a weak partial agonist at the κ-opioid receptors, with the highest binding affinity at μ-opioid receptors. PEGylation reduces the passive permeability of the drug, and also renders the compound a substrate for the P-glycoprotein (P-gp) transporter. This ABC efflux transporter is highly expressed at the luminal (apical) membrane of brain capillary endothelial cells and serves as a defence mechanism to limit penetration and accumulation of naturally occurring toxins, xenobiotics, and drugs into the brain. Due to poorer permeability and increased efflux of naloxegol across the blood brain barrier related to P-gp substrate properties, the central nervous system (CNS) penetration of naloxegol is minimal.

In the present submission, AstraZeneca Pty Ltd seeks to register immediate release film coated tablets containing naloxegol (as oxalate) 12.5 mg and 25 mg under the trade name "Movantik", to be administered on an empty stomach at a recommended maximum daily dose of 25 mg.

Drug substance (active ingredient)

Naloxegol oxalate (designated NKTR-118 oxalate or AZ13337019 oxalate by the company; structure reproduced in Figure 1) has 5 chiral centres (C-5, C-6, C-9, C-13, C-14), for which the absolute configuration is 5S, 6S, 9R, 13S, 14S. Four of the five chiral centres are associated with the starting material naloxone hydrochloride and one with the axial orientation of methoxy(hepta-ethylene glycol)-oxy bond (designated "5α,6α").

Figure 1. Chemical structure of naloxegol oxalate.



The drug substance is manufactured by a complex, convergent synthesis.

Two non-solvated polymorphic forms are described in the dossier (Forms A and B), of which that designated Form B is the only form that can be obtained under proposed commercial manufacturing conditions.

The drug substance is BCS Class 3; whilst highly soluble (> 50 mg/mL) across the physiological pH range, permeability data assessed across Caco-2 cell monolayers indicate the drug substance has low permeability.

The dossier states that naloxegol oxalate exhibits 2 pKa values: 8.4 (amine) and 9.5 (phenol), and that LogP = 1.4 in octanol/water.

No limits are applied to the particle size distribution of the drug substance due to its high aqueous solubility, and because variability in the particle size distribution also had no impact on tablet hardness, content uniformity or overall finished product stability.

The chirality of the drug substance is not controlled in the active pharmaceutical ingredient (API) specification.

Six potential impurities are controlled in the drug substance. Limits for these have been accepted on the advice of the toxicology evaluator.

A number of issues relating to the quality control of the naloxegol oxalate drug substance were raised with the sponsor; all have been resolved.

Drug product

Both strength tablets are oval, biconvex, mauve, film coated tablets debossed with "nGL" on one side. The 12.5 mg and 25 mg tablets are debossed with "12.5" and "25" respectively on the other side. The tablets will be marketed in OPA/aluminium/PVC/aluminium blisters.

Early Phase I clinical studies were conducted using a tablet containing 100 mg of naloxegol free base. Naloxegol oxalate was used as the active ingredient in all subsequent tablet batches except for a 12.5 mg and a 25 mg tablet formulation used in Phase III studies.

Bridging studies were conducted under different dissolution conditions to confirm the equivalence of the *in vitro* dissolution profiles of the Phase III naloxegol 12.5 mg and 25

mg (as free base) film coated tablets in the 3 different media with those of the proposed commercial 25 mg and 12.5 mg formulations containing naloxegol (as oxalate), and another to show that the results generated with the USP Apparatus 1 (900 mL, 100 rpm) are equivalent to results obtained using the USP Apparatus 2 (500 mL, 50 rpm). A third study was performed which showed that the proposed commercial formulation manufactured from API synthesised using a slightly different crystallisation process has identical dissolution profiles across the physiological pH range to those obtained from the corresponding tablets manufactured from API synthesised using the proposed commercial process, in both cases using the proposed regulatory method.

As the quantity of the drug substance reported dissolved after 15 minutes corresponded to the total quantity of drug substance present as determined by the assay using the chosen method, the company was requested to apply a more discriminatory sampling time (20 minutes), but declined on the grounds that

> *The dissolution profile of naloxegol film-coated tablets does not significantly affect the bioavailability, the dissolution conditions and acceptance criteria are therefore set to pass clinically acceptable batches. The proposed specification is suitable to guarantee consistent bioavailability of commercial batches and provide verification of manufacturing process consistency as part of the control strategy … and follows the guidance of ICH 6QA.*

The proposed acceptance criterion "Q = 80% of Label Claim dissolved after 30 minutes" was accepted on this basis.

The stability data in the original dossier support respective default shelf lives of 18 months and 12 months stored below 30°C for the 12.5 mg and 25 mg tablets packaged in the OPA/aluminium/PVC/aluminium blisters proposed for Australia. However, based on the company's regression analysis of data concurrently generated from tablets stored at 25°C/60% RH, an alternative shelf life of 24 months stored below 25°C was offered to the company for the 12.5 mg and 25 mg tablets on a risk management basis. After initially declining this offer and instead submitting further stability data which were claimed to support the shelf life of 24 months stored below 30°C for both strength tablets originally requested, AstraZeneca has since accepted the alternative shelf life of 24 months stored below 25°C after being advised that the new stability data would not been accepted for evaluation under TGA business rules.

An issue raised with the company regarding the *Assay* test procedure (for both naloxegol oxalate and propyl gallate) remains unresolved.[2]

Biopharmaceutics

Three relative bioavailability and bioequivalence clinical studies were conducted to create a link between the various naloxegol formulations that have been used during clinical development; Study 08-PNL-04, Study D3820C00025 and Study D3820C00018. Details of these are presented below.

Relative bioequivalence study (Study 08-PNL-04)

This was a single dose, open label, randomised, 2 way crossover study for which the primary objective was to assess the relative bioavailability of 100 mg film coated naloxegol (as free base) tablet compared to 100 mg naloxegol (as free base) oral aqueous solution (4%). The 90% confidence interval (CI) of the ratio of the geometric least squares (LS) means (reproduced below) was completely contained in the 80.00% to 125.00% interval for $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, and Cmax, suggesting that the tablet formulation was

[2] It is acknowledged that this issue was later resolved.

bioequivalent with the oral solution. Furthermore, the study results show that for the investigated tablet formulation, in vivo dissolution is not limiting the rate or extent of absorption of naloxegol compared to an oral solution.

Table 2: Study 08-PNL-04.

Parameter	Units	N[a]	Test Mean[b] (NKTR-118 Tablet)	Reference Mean[b] (NKTR-118 Solution)	Test/ Reference[c]	90% Confidence Interval[d]
C_{max}	ng/mL	20	215	212	101	(85.00 , 120.81)
$AUC_{(0\text{-last})}$	ng·hr/mL	20	713	680	105	(95.18 , 115.64)
$AUC_{(0\text{-inf})}$	ng·hr/mL	20	717	684	105	(95.20 , 115.54)

Study Population: PK

[a] N was the number of subjects with evaluable PK data for both treatments.

[b] Least squares mean from ANOVA. Calculated by transforming the least squares means in natural log scale back to the linear scale (i.e., geometric means).

[c] Ratio of geometric means (expressed as a percent) is calculated by transforming the difference in least squares mean in natural log scale to linear scale and then multiply by 100.

[d] 90% confidence interval for ratio of geometrics means (expressed as a percent), is calculated by transforming the 90% confidence interval around difference in least squares means in log scale to linear scale.

Relative bioavailability/food effect study (Study D3820C00018)

This was an open label, randomised, single dose, 3 period crossover study for which the primary objective was to assess the bioequivalence with respect to Cmax and AUC of one 25 mg naloxegol (as oxalate) commercial formulation tablet and one 25 mg naloxegol (as free base) Phase III formulation tablet following administration of a single dose to healthy adult male and female subjects under fasting conditions. The secondary objective was to assess the effect of food on the pharmacokinetics (PK) of 25 mg naloxegol (as oxalate) commercial formulation film coated tablets. The 90% CI of the ratio of the geometric LS means for the primary assessment (reproduced below) was completely contained in the 80.00% to 125.00% interval for $AUC_{(0\text{-t})}$, AUC, $AUC_{(0\text{-24h})}$ and Cmax, suggesting that the two tablet formulations were bioequivalent with respect to these parameters in relation to administration of a single dose in the fasted state.

Table 3: Statistical comparison of primary PK parameters for Treatments A and C (fasted state).

						Comparisons		
Parameter (Units)	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI (%)**	**Pair**	**Ratio (%)**	**90% CI (%)**
AUC (ng·h/mL)	A	Fasted	42	144.6	(126.56, 165.33)	A/C	94.38	(89.13, 99.94)
	C	Fasted	41	153.3	(134.05, 175.22)			
$AUC_{(0-t)}$ (ng·h/mL)	A	Fasted	42	142.4	(124.48, 162.80)	A/C	93.98	(88.67, 99.60)
	C	Fasted	41	151.5	(132.42, 173.28)			
$AUC_{(0-24)}$ (ng·h/mL)	A	Fasted	42	140.5	(123.16, 160.20)	A/C	93.66	(88.38, 99.25)
	C	Fasted	41	150.0	(131.46, 171.10)			
C_{max} (ng/mL)	A	Fasted	42	38.35	(33.13, 44.39)	A/C	92.38	(82.42, 103.54)
	C	Fasted	41	41.51	(35.82, 48.10)			

CI: Confidence interval; Geo: Geometric; IR: Immediate release; LS: Least squares; Tmt: treatment
Results based on linear mixed effect analysis of variance model with terms for sequence, period, and treatment as fixed effects, and volunteer within sequence as a random effect.
[a] Treatment A: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fasted condition).
[a] Treatment C: Single oral administration of naloxegol film-coated IR tablet 25 mg Phase III formulation (fasted condition).

However, the 90% CI of the ratio of the geometric LS means for the secondary assessment (reproduced below) was not contained in the 80.00% to 125.00% interval for any of these parameters, indicating that $AUC_{0-\infty}$ and Cmax are increased by 45% and 29.5% (respectively) when the commercial formulation 25 mg naloxegol (as oxalate) film coated tablet is taken in the presence of food.

Table 4: Statistical comparison of primary PK parameters for Treatments B and A (fed versus fasted state).

						Comparisons		
Parameters	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI (%)**	**Pair**	**Ratio (%)**	**90% CI (%)**
AUC (ng·h/mL)	A	Fasted	42	144.6	(126.56, 165.33)	B/A	145.09	(137.09, 153.56)
	B	Fed	42	209.9	(183.62, 239.87)			
$AUC_{(0-t)}$ (ng·h/mL)	A	Fasted	42	142.4	(124.48, 162.80)	B/A	145.72	(137.56, 154.35)
	B	Fed	42	207.4	(181.39, 237.22)			
$AUC_{(0-24)}$ (ng·h/mL)	A	Fasted	42	140.5	(123.16, 160.20)	B/A	143.60	(135.58, 152.10)
	B	Fed	42	201.7	(176.86, 230.05)			
C_{max} (ng/mL)	A	Fasted	42	38.35	(33.13, 44.39)	B/A	129.51	(115.66, 145.02)
	B	Fed	42	49.66	(42.90, 57.49)			

CI: Confidence interval(s); Geo: Geometric; IR: Immediate release; LS: Least squares; n: Number of observations; Tmt: Treatment
Results based on linear mixed effect analysis of variance model with terms for sequence, period, and treatment as fixed effects, and volunteer within sequence as a random effect.
[a] Treatment A: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fasted condition).
[a] Treatment B: Single oral administration of naloxegol film-coated IR tablet 25 mg commercial formulation (fed condition).

Relative bioavailability/food effect study (Study D3820C00025)

This was a Phase I, open label, randomised, balanced, single dose, 2 part study to assess the relative bioavailability of naloxegol (as oxalate) in 3 formulations under fasted (3 way crossover) and fed (2 way crossover) conditions in male and non-fertile female subjects, for which the primary objective was to assess the relative bioavailability of two 25 mg naloxegol (as oxalate) new formulation uncoated tablets ["Variant Fast" (Formulation 1)

and "Variant Slow" (Formulation 2)] and one 25 mg naloxegol (as free base) Phase III formulation film coated tablet (Formulation 3) following administration of a single dose to healthy adult male and female subjects in the fasted state. The secondary objectives were to:

- Assess the relative bioavailability of new naloxegol (as oxalate) Formulation 1 to Formulation 2 following single oral dose administration in healthy adult volunteers under fasted conditions.
- Assess the effect of food on the PK of the new naloxegol (as oxalate) Formulation 1 and the naloxegol (as free base) Phase III formulation following single oral dose administration in healthy male and non-fertile female volunteers.

The company's 90% CIs of the geometric mean ratios for each of the primary PK parameters for Formulations 1, 2 and 3 (reproduced below) fell within the pre-established range for bioequivalence as defined in the study protocol.

Table 5: Statistical comparison of primary PK parameters for Formulations 1, 2 and 3 (fasted state).

						Comparisons		
Param	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC	Form 1	Fasted	22	161.3	(137.3, 189.4)	Form 1/Form 3	106.46	(97.29, 116.50)
(ng·h/mL)	Form 2	Fasted	24	156.2	(133.3, 183.0)	Form 2/Form 3	103.12	(94.41, 112.64)
	Form 3	Fasted	23	151.5	(129.1, 177.7)	Form 1/Form 2	103.24	(94.36, 112.96)
C_{max}	Form 1	Fasted	22	33.77	(27.62, 41.30)	Form 1/Form 3	99.98	(88.26, 113.25)
(ng/mL)	Form 2	Fasted	24	32.93	(27.03, 40.12)	Form 2/Form 3	97.48	(86.28, 110.14)
	Form 3	Fasted	23	33.78	(27.67, 41.23)	Form 1/Form 2	102.56	(90.56, 116.15)

CI confidence interval; Geo geometric; IR immediate release; LS least squares; Param parameters; Tmt treatment; WFC white film-coated.

[a] Form 1: 25 mg NKTR-118 IR Variant Fast Oxalate (Formulation 1)
Form 2: 25 mg NKTR-118 IR Variant Slow Oxalate (Formulation 2)
Form 3: 25 mg NKTR-118 (reference, WFC tablet, F13775, Formulation 3)

The point estimates of the geometric LS mean ratios and associated 90% CI for naloxegol $AUC_{0-\infty}$ and Cmax for Formulations 1 and 3 (fed versus fasting comparisons),together with a statistical analysis of these result, are reproduced below.

Table 6: Statistical comparison of primary PK parameters for Formulations 1 and 3 (fed versus fasted state).

						Comparisons	
Param	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC	Form 1	Fasted	22	161.0	(138.7, 187.0)			
(ng·h/mL)		Fed	20	228.1	(195.4, 266.4)	Fed/Fasted	141.69	(129.27, 155.31)
	Form 3	Fasted	23	150.5	(127.6, 177.5)			
		Fed	21	234.0	(197.5, 277.2)	Fed/Fasted	155.47	(137.84, 175.36)
C_{max}	Form 1	Fasted	22	33.26	(28.25, 39.16)			
(ng/mL)		Fed	20	44.79	(37.68, 53.24)	Fed/Fasted	134.65	(113.81, 159.30)
	Form 3	Fasted	23	33.38	(27.16, 41.03)			
		Fed	22	48.96	(39.72, 60.35)	Fed/Fasted	146.66	(124.76, 172.42)

CI confidence interval; Geo geometric; IR immediate release; LS least squares; Param parameters; Tmt treatment; WFC white film-coated.

[a] Form 1: 25 mg NKTR-118 IR Variant Fast Oxalate (Formulation 1)
Form 2: 25 mg NKTR-118 IR Variant Slow Oxalate (Formulation 2)
Form 3: 25 mg NKTR-118 (reference, WFC tablet, F13775, Formulation 3)

Table 7: Statistical comparison of primary PK parameters for Formulations 1 and 3 (fed state).

							Comparisons	
Param	**Tmt[a]**	**State**	**n**	**Geo LS mean**	**95% CI**	**Pair**	**Ratio (%)**	**90% CI**
AUC	Form 1	Fed	20	227.2	(199.5, 258.9)	Form 1(Fed)/ Form 3(Fed)	95.40	(89.97, 101.17)
(ng·h/mL)	Form 3	Fed	21	238.2	(209.4, 271.0)			
Cmax	Form 1	Fed	20	44.72	(37.91, 52.74)	Form 1(Fed)/ Form 3(Fed)	90.31	(78.99, 103. 24)
(ng/mL)	Form 3	Fed	22	49.52	(42.34, 57.90)			

CI confidence interval; Geo geometric; IR immediate release; LS least squares; Param parameters; Tmt treatment; WFC white film-coated.

[a] Form 1: 25 mg NKTR-118 IR Variant Fast Oxalate (Formulation 1)
Form 3: 25 mg NKTR-118 (reference, WFC tablet, F13775, Formulation 3)

The study report states:

> *In the fed state, for Formulations 1 and 3, the geometric mean $t_{½(\lambda z)}$ was prolonged to 9.09 and 9.83 hrs, respectively compared to 8.31 and 7.74 h in the fasted state. This may be a result of the 40% to 50% higher exposure following food administration which resulted in a longer quantifiable terminal phase secondary to the higher exposure. There is an apparent correlation between the last time point at which NKTR-118 concentrations are still quantifiable and the magnitude of $t_{½(\lambda z)}$. However, since $AUC_{(0-t)}$ accounted for the majority of $AUC_{0-\infty}$ (97% to 99% in the fasted and fed states, respectively), the apparent differences in $t_{½(\lambda z)}$ between the fasted state and the fed state for Formulations 1 and 3 do not seem to be of any relevance.*

Quality summary and conclusions

There are no objections in respect of Biopharmaceutics to registration of these products. However, a matter relating to the quality control of the finished products requires resolution before approval can be recommended from a Quality perspective.[3]

III. Nonclinical findings

Introduction

AstraZeneca Ltd. has submitted a generally high quality nonclinical dossier for the registration Movantik (naloxegol, as oxalate) as a new chemical entity for the management of OIC. Naloxegol is intended to specifically treat OIC in the periphery with minimal effects on centrally mediated opioid-induced analgesia. OIC is a common and undesirable effect of opioid pain therapy with up to one-third of treated patients reporting the effect. The distress caused by OIC can rival or exceed that caused by the pain that triggered the need for opiate therapy in the first place. Accordingly, there is a need for agents that can control OIC without disrupting the CNS associated pain relieving actions of opiates. The sponsor claims that naloxegol fulfils this need.

Pharmacology

Primary pharmacology

Naloxegol is a PEGylated derivative of the μ-opioid receptor antagonist naloxone. Naloxegol is also a neutral antagonist of κ- and δ-opioid receptors. α-PEGylation (α-PEG≥5) of naloxone greatly reduces its blood brain barrier (BBB) penetrance, in part by making it an ABC B1 efflux transporter substrate. Accordingly naloxegol mostly acts on peripheral opioid receptors with minimal CNS effects, provided there is effective BBB ABC B1 efflux transporter activity.

In vitro PEGylation of naloxone to produce naloxegol retains the high affinity at μ- opioid receptors (> 98% inhibition of agonist receptor binding at a concentration of 10 μM), but results in an altered selectivity profile (naloxegol order of affinity is μ > δ > κ compared with naloxone order of affinity-y of μ > κ > δ). PEGylation of naloxone to produce naloxegol results in a reduction of affinity of ≈ - 47x at κ-opioid receptors and ≈ - 5.2x at δ-opioid receptors. Naloxegol displays no agonist activity at cloned human μ opioid receptors in vitro. Naloxegol displayed no agonist activity at κ-receptors in the field stimulated rabbit vas deferens at concentrations ≤ 1.0 x 10-5 M. As expected, naloxegol displays potent inhibition of both [D-Ala2, NMe-Phe4, Gly-ol5]-enkephalin and morphine activity with a mean % relative Imax ± SD values of 85.69 ± 2.66 and 85.95 ± 8.85, respectively and a mean pIC50 ± SD values of 6.64 ± 0.05 and 7.25 ± 0.15, respectively.

In rat models, oral naloxegol (9:1 oral naloxegol to intravenous [IV] morphine dose ratio) effectively reversed opiate-induced small intestinal ileus in SD rats in vivo. However, naloxegol is less effective at reducing opiate-induced ileus compared with oral naloxone. Unlike naloxone, naloxegol at low oral naloxegol:IV morphine dose ratios largely acts in the periphery with minimal to no effects on opiate-induced central analgesia. High oral naloxegol:IV morphine dose ratios (18:1) slightly reduced opiate-induced analgesia as measured by the rat hotplate withdrawal test.

[3] It is acknowledged that this issue was later resolved.

Secondary pharmacodynamics and safety pharmacology

Naloxegol displays substantial inhibition of agonist binding at δ- and κ-opioid receptors in vitro (90 and 97% inhibition of agonist receptor binding at a concentration of 10 μM, respectively). Some inhibition (25%) of agonist receptor binding at adenosine A2A receptors in vitro was noted at 10 μM.

Naloxegol was not analgesic in the mouse grid stimulation analgesia test.

Naloxegol is largely inactive at voltage-gated cardiac ion channels in vitro. Naloxegol increased hERG current by (mean ± SEM; n = 3) 16.0 ± 1.7% at 10 μM, 25.9 ± 0.6% at 30 μM and 7.9 ± 0.6% at 100 μM and inhibited hERG current by 13.3 ± 0.4% at 300 μM vs 0.4 ± 0.1% in control. The hERG increase at 10, 30, 100 μM and inhibition at 300 μM was statistically significant ($P<0.05$) when compared to vehicle control values. The IC50 for the inhibitory effect of naloxegol on hERG potassium current was estimated to be > 300 μM. Given that the Cmax for naloxegol is 81.1 ng/mL equating to ≈ 0.11μmol/L, naloxegol is unlikely to produce biologically significant QT prolongation under conditions of clinical use. Based on the available in vitro and canine data, the risk of Torsade de Pointes under conditions of human clinical use is low.

In dogs, naloxegol produced negative effects on systemic systolic, diastolic blood pressure and left ventricular systolic pressure, tachycardia (presumably compensatory reflex responses to lowered blood pressures), and transient PR interval elongation, at ≥25 mg/kg per os (PO) (plasma Cmax ≥0.829 μmol/L, ca 7.5x clinical Cmax). The apparent NOAEL for cardiovascular effects was 5 mg/kg PO (plasma Cmax 0.152 μmol/L, ca 1.4x clinical Cmax). However, these effects were not replicated in the canine repeat dose studies. Thus effects seem unlikely to occur under human clinical use conditions. There were no effects on cardiac function (including coronary arterial flow and inotropic effect) in an isolated perfused rat heart model at concentrations up to 10 μM (ca 90x clinical Cmax), implying little potential for adenosine A2A receptor antagonist induced effects on cardiac perfusion under clinical use conditions. There was also no effect on isolated canine myocyte contractility parameters (up to 100 μM), and hERG channel effects were modest and not concentration dependent (concentration range tested 10-300 μM).

Supra therapeutic oral doses of naloxegol produced delayed gastric emptying and paradoxical small intestinal ileus. The no observed adverse effect level (NOAEL) for delayed gastric emptying was 30 mg/kg PO (NOAEL ≈ 11x human clinical dose) and the NOAEL for induction of small intestinal ileus was 300 mg/kg PO (>100x human clinical dose).

Naloxegol does not induce opiate dependence associated physical withdrawal syndromes in rodents and does not induce physical dependence. The no observed effect level (NOEL) for acute physical withdrawal effects was 50 mg/kg, while the NOEL for physical dependence was ≥ 500 mg/kg. Naloxegol does not exacerbate drug (cocaine) seeking behaviour and does not display potential for addiction or central μ-receptor psychoactive effects in rats. However, naloxegol at 300 mg/kg caused a partial to complete reversal of the discriminative effects of morphine with no substantial effects on response rates, demonstrating the ability of naloxegol to reach the CNS and produce subtle μ-opioid receptor antagonist effects on addictive behaviours in rats (NOAEL > 3 mg naloxegol/kg PO, ≈ the human clinical dose).

Pharmacokinetics

Absorption

The oral systemic bioavailability in animal studies was generally low, but dose dependent (in dogs where absolute bioavailability [F_{Abs}] increases by ≈ 2-2.5x at oral doses > 2 mg/kg body weight). The dose dependency likely reflects saturation of enterothelial ABC B1 efflux

transporters. Potential drug-drug interactions with naloxegol may occur at this transporter (NOAEL in dogs is ≈ 2 mg/kg; ≈ 2x human clinical dose). Additionally, naloxone inhibits OATP1A2 efflux transporters (resembles the effects of naringin in grapefruit juice; another potential cause of drug-drug interactions); however it is unknown if naloxegol produces similar effects.[4] Inhibition of enterothelial OATP1A2 efflux transporters is a well known cause of drug interactions. Enterothelial efflux transporter drug-drug interactions were evaluated in the dossier.

Consistent with the available human data, oral administration of naloxegol in non-fasted cynomolgus monkeys predictably increases the bioavailability and the Cmax of the tablet dose form of naloxegol ($AUC_{Non\text{-}Fasted}$:AUC_{Fasted} ≈ 1.8 and $Cmax_{Non\text{-}Fasted}$:$Cmax_{Fasted}$ ≈ 1.8). In rats, a sex difference in oral absorption is apparent. Females consistently have lower Tmax (2-6x lower), higher Cmax (≈ 2x higher) and higher $AUC_{0\text{-}\tau}$ (≈ 2x higher) than males. These differences are consistent with known sex differences in enterothelial ABC B1 efflux transporters in rats.[5] Sex differences were not apparent in dogs and the effect is likely species specific.

In animals, the plasma clearance of the parent drug is high. The $t_{½}$ of the parent is relatively short (in dogs following IV injection overall plasma clearance ≈ 2.6 L/h/kg; $t_{½}$ ≈ 5.7 h). However, a trend towards a slightly lower $t_{½}$ as the oral dose increases is apparent in dogs, implying that the β elimination phase may not follow simple 1st order elimination kinetics in this species. In rats, single dose IV naloxegol displays a decreased $t_{½}$ as the dose increases, again implying that the β elimination phase does not obey simple 1st order kinetics. The short oral $t_{½}$ implies that plasmatic accumulation would not normally occur with the proposed clinical OID dosing regimen. However, elimination largely depends on a single route of excretion, increasing the risk of biliary disease associated reductions in clearance. Notably, at systemic exposures that greatly exceeded those associated with human clinical use, evidence for plasmatic accumulation (generally ≈1.5-2x) was noted in dogs and rats. Evidence of zero order elimination kinetics was associated with these findings, thus plasmatic accumulation is more likely a feature of saturation elimination kinetics and probably only relevant under overdose conditions.

Distribution

Consistent with its rapid clearance, naloxegol is highly unbound to plasma proteins. In radiotracing studies, blood:plasma ratios were consistently <0.8 across species implying that radioactivity of drug origin was mostly associated with plasma and not erythrocytes. Based on rat autoradiography, naloxegol associated radioactivity displays an affinity for melanin with high accumulation in the uveal tract. Naloxegol associated radioactivity also distributes to pigmented skin. Other important sites of distribution of naloxegol associated radioactivity are liver, kidneys, and glandular tissues such as the adrenals, Harderian, pituitary, preputial, salivary and thyroid glands. Critically, the level of radioactivity in brain and spinal cord remained below measurable limits in males. In females, the level of radioactivity in maternal brain was higher than in males but brain and spinal cord contained the lowest levels of all tissues measured. Radioactivity in the maternal brain and spinal cord was cleared to undetectable levels at >4 to ≤24 h. As expected, foetal brain radioactivity levels are somewhat higher than maternal brain levels and the rate of concentration decline is slower. However, foetal brain radioactivity was cleared to undetectable levels at >4 to ≤24 h.

The pattern of absorption and distribution was different in male and female rats. The maximum concentration in the majority of tissues was observed at 0.5 h post dose (the

[4] Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol. 2009 Oct; 158(3):693-705.
[5] Mariana B, Adrián L, Guillermo V, Juan S, Laura M, Carlos L. Gender-related differences on P-glycoprotein-mediated drug intestinal transport in rats. J Pharm Pharmacol. 2011 May; 63(5):619-26.

first time point) for female rats and at 1h post-dose (the second sampling time point) for male rats. Tissue concentrations were higher in the female than the male rats at the same time-points, consistent with higher Cmax and lower Tmax in females.

In both sexes, elimination of radioactivity was rapid, with the majority of tissues containing levels of radioactivity below the limit of reliable measurement by 24 h post dose. Critically the degree of CNS uptake is dependent on the length of the PEG moiety. Minimal penetrance of the CNS is associated with $PEG_{\geq 5}$ (Δ PEG_5-PEG_3 results in ≈ 5x increase in PEG_X-naloxone in the CNS).

Metabolism

The bulk of radioactivity associated with oral administered naloxegol is excreted unchanged in the faeces in most species due to a combination of lack of absorption and hepatobiliary excretion. The absorbed naloxegol fraction is rapidly metabolised mostly by limited O-dealkylation/oxidation of the PEG chain and/or O-glucuronidation predominantly at C3 of the naloxone moiety. This results in a large number of observable metabolites, mostly due to changes in the length of the PEG chain. Minor pathways of metabolism include O-demethylation, N-oxidation, sulfation, oxidation of the naloxone-core of the molecule, oxidation with breaking of the tetrahydrofuran ring and formation of a cysteine conjugate. All metabolites found in human samples have also been observed in animals, although species differences are apparent. Comparison of pooled plasma samples from rats, dogs and humans at steady state showed 4 significant circulating metabolites (M1, M7, M10 and M13) for which AUC multiples at the NOAEL of 6-205x were demonstrated. Naloxegol-glucuronide (M2), a major animal metabolite, is not a significant metabolite in humans. In humans, naloxegol glucuronide is only detectable at oral doses ≈ 10x the proposed maximum human clinical daily dose. At this level of exposure the maximum exposure to naloxegol glucuronide in humans is < 1% of the circulating naloxegol levels and at the human clinical dose of 25 mg/day, the glucuronide is ≈1% of the naloxegol AUC. *In vitro* studies demonstrated that phase I metabolism is catalysed predominantly by CYP3A4/5 with minor contributions by CYP2D6 (responsible for the formation of M9). The limited spectrum of CYP isoforms involved in the metabolism of naloxegol increases the risk of victim/perpetrator types of drug-drug interactions.

Excretion

Excretion of radioactivity associated with oral treatment with ^{14}C naloxegol is rapid in rats and dogs, the majority of radioactivity being excreted within 48-72 h post exposure with minimal retention of radioactivity within the carcasses. The major pathway of excretion was in faeces (≈63-80% of the administered radioactivity in males and ≈ 66% in females). Bile duct ligation and urinary excretion studies demonstrated that ≈ 66-80% of the orally administered radioactivity was systemically absorbed under high (over) dose conditions and that biliary excretion is a major route of elimination in rats. Urinary excretion accounted for ≈ 20% of the administered dose in male rats, ≈ 30% in female rats and ≈ 25% in dogs. Elimination of radioactivity was slightly slower in females; however excretion was mostly complete at 48 h post-dosing. Total plasma radioactivity of drug origin was ≈ 20x that of the naloxegol parent drug, implying high systemic exposure to circulating naloxegol metabolites. The terminal $t_{½}$ attributable to drug derived radioactivity was ≈ 2x that of the parent drug demonstrating the presence of a longer duration of systemic exposure to drug metabolites compared with the parent drug.

Other studies

The log P for naloxegol is 1.43 ± 0.03. Naloxegol has two pKa values of 8.45 ± 0.01 and 9.48 ± 0.06, consistent with its two ionisable centres. Naloxegol is stable in rat and human plasma for > 22-23 h at 37C.

Conclusions

Naloxegol PK in animals was an adequate model for the assessment of drug toxicity in humans.

Pharmacokinetic drug interactions

Oral systemic bioavailability in animal is affected by dose-dependent saturation of enterothelial ABC B1 efflux transporters. Potential drug-drug interactions with naloxegol may occur at this transporter (no-effect dose for saturation in dogs is ≈ 2 mg/kg; ≈ 0.05x human clinical dose). Additionally, naloxone inhibits OATP1A2 efflux transporters (resembles the effects of naringin in grapefruit juice; another potential cause of drug-drug interactions); however it is unknown if naloxegol produces similar effects (although it is likely).[6] In response to a Section 31 question regarding potential naloxegol-OATP1A2 interactions, the sponsor acknowledged the presence of OATP1A2 in the gut and noted that naloxone can inhibit OATP1A2 under *in vitro* conditions, but could not locate any clinical studies demonstrating an effect of naloxone on OATP1A2 substrates *in vivo*. The sponsor considers interactions with naloxegol at OATP1A2 transporters unlikely (although no data have been provided to support this claim). The clinical effects of enterothelial efflux transporter drug-drug interactions were evaluated in greater detail in Module 5 of the dossier.

Naloxegol-induced inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 is unlikely to be significant under clinical use conditions. Naloxegol is not an inducer of hepatic microsomal CYP1A, CYP2B, CYP3A and CYP4A.

Toxicology

Acute toxicity

Naloxegol as the free base has low acute oral toxicity in rats with a maximum non-lethal dose ≥ 2000 mg/kg body weight (BW) and ≥ 1000 mg/kg BW for the oxalate salt. Transient signs of ill thrift and palatability effects were noted in rats at doses ≥ 1000 mg/kg BW for the oxalate form (naloxegol).

Repeat dose toxicity

The supplied oral repeat dose toxicity studies were adequate for assessment purposes and were generally consistent with current guidance. Overall, repeated oral exposure to naloxegol was well tolerated by the species evaluated. PK and test article tolerance sex associated differences were noted in the rat studies. These differences were either not apparent or less apparent in the other species evaluated. The most consistently observed adverse effects were consistent with a glucocorticoid generalised stress response, particularly in rodents. Possible equivocal evidence of hepatocyte cannalicular/apical membrane leakage was present in one rodent study. Neurotoxicity/neurobehavioural toxicity was observed in the high dose group in the 39 week dog study.

Relative exposure

Relative exposure in repeat-dose toxicity and carcinogenicity studies are shown in Table 8.

[6] Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. *Br J Pharmacol.* 158: 693-705 (2009).

Table 8: Relative exposure in repeat-dose toxicity and carcinogenicity studies.

Species	Study duration	Dose (mg/kg/day)	Mean AUC_{0-24h} at Study Termination or Last Sample Time Point (µg·h/mL)		Exposure ratio#	
			Male	Female	Male	Female
Mouse	3 months (LS-2007-056)	50	1.73	1.84	5	5
		400*	16.3	16.0	45	44
		600	60.2	44.6	165	123
		800	38.2	79.5	105	219
	2 year (LS-2008-006)	25	3.96	3.00	11	8
		70/50†	7.30	6.01	20	17
		200/100†* (males) 400/160†* (females)	14.10	8.86	39	24
Rat (SD)	7 days (LS-2007-005)	100*	13.1	53.4	36	147
		1000	401.0	595.0	1102	1635
	28 days (LS-2007-011)	50	5.5	25.1	15	69
		150	29.3	95.3	81	262
		500*	262.7	372.0	722	1022
	3 months (LS-2007-028)	50	11.3	36.4	31	100
		400	252	367	693	1009
		600 (*males)	337	474	926	1303
		800 (*females)	478	580	1314	1594
	26 weeks (LS-2007-040)	50	9.17	29.7	25	82
		200 (*male)	82.0	127	225	349
		800 (*female)	389	524	1069	1440
	2 year (LS-2008-007)	40*	16.8	35.7	46	98
		120	81.1	106.0	223	291
		400	270.0	340.0	742	934
Dog (Beagle)	14 days (LS-2007-004)	200	20.2	24.7	56	68
		500*	90.7	65.7	249	181
	28 day (LS-2007-012)	50	3.9	3.1	11	8
		150	14.7	11.5	40	32
		500	64.4	62.8	177	172
	39 weeks (LS-2007-041)	50	13.3	11.7	37	32
		200*	54.4	57.4	150	158
		500	194	205	533	563
Transgenic animals (Tg.rasH2 wild-type mice; -ve control for Tg.rasH2 mice)	28 days (10-2216)	150*	39.1	19.1	107	52
		500	127.6	68.2	350	187
		1500	408.7	281.9	1123	775

Species	Study duration	Dose (mg/kg/day)	Mean $AUC_{0-24\,h}$ at Study Termination or Last Sample Time Point (µg·h/mL)	Exposure ratio#	
Human (healthy volunteers, mixed sex) Study 07-IN-NX002	steady state	25	0.3639	--	--

* NOAEL
# animal:human plasma $AUC_{0-24\,h}$
† Dose adjusted at day 117/118 due to excessive premature mortality

Major toxicities

Overall naloxegol is well tolerated in repeat dose toxicity studies at exposures that substantially exceed expected human clinical systemic exposures (based on plasma AUC ratios). All human relevant adverse effects occurred at > 25x human clinical systemic exposure (based on AUC ratios).

In terms of non-carcinogenic effects, rodent glucocorticoid generalised stress responses were the most consistently observed adverse effect. Consistent with this was the detection of reduced reticulocyte counts in the absence of any other erythro-dyscrasias in rats. Naloxone is known to attenuate stress induced bone marrow erythrohyperplasia in rodents and reduced circulating reticulocytes are consistent with this type of effect.[7] The effect is of doubtful human relevance. Reduced uterine weight and uterine atrophy, also consistent with the rodent chronic glucocorticoid generalised stress responses, was noted in one study. Non adverse to adverse reductions in BW and/or BW gain (often correlated with reduced food intake) were consistently observed across studies (possibly correlated with delayed gastric emptying).

Equivocal evidence of hepatocyte cannalicular/apical membrane leakage was present in one rodent study. Neurotoxicity/neurobehavioural toxicity was observed at extreme doses (> 1000x clinical Cmax, > 500x clinical AUC) in the 36 week dog study.

Naloxegol is a nasopharyngeal epithelial toxicant following sub-acute repeat daily dosing of mice at supratherapeutic doses (> 70x human clinical systemic exposure on an AUC ratio basis). The changes affected the respiratory epithelium lining the nasal septum, the transitional zone of the epithelium as it changes from squamous to respiratory (vestibule), and the transitional zone where the epithelium changes from respiratory to olfactory epithelium. The degenerative changes also affected the olfactory epithelium, predominantly the epithelium overlying the scrolls. Moderate to severe changes were also seen in the respiratory epithelium lining the nasopharynx. Erosion of the respiratory mucosa was occasionally present. Degenerative changes in the nasopharyngeal mucosa were similar to changes in the respiratory epithelium of the nasal septum and scrolls. The specific mode of action of these effects was not identified; however the damage most likely resulted from local metabolic toxication.

Genotoxicity

The potential for directly DNA interacting mutagenesis by naloxegol and/or its S9 metabolites was examined in vitro in bacterial reverse mutation assays and in forward mutations in mammalian cells as well as in vivo in the mouse bone marrow micronucleus

[7] Zakharova OI, et al. The participation of opiatergic mechanisms in the regulation of bone marrow hematopoiesis in stress. *Patol Fiziol Eksp Ter.* Nov-Dec;(6): 11-14 (1989).

test. All assays were of acceptable design and quality, and were consistent with ICH S2A,[8] ICH S2B,[9] and relevant Organisation for Economic Co-operation and Development (OECD) test guidelines and test acceptance criteria. Naloxegol was not classically mutagenic or clastogenic in the mammalian cell forward mutation assay or in the mouse bone marrow micronucleus test.

No evidence of mutagenicity was observed in bacterial reverse-mutation assays when naloxegol was tested as the oxalate salt. However a clearly mutagenic and genotoxic degradant, glycidaldehyde, was present in a number of batches of free base naloxegol. Use of the naloxegol oxalate salt that has been stored in the solid state protects naloxegol from degradation and release of glycidaldehyde. Other genotoxic impurities are present in Movantik (see Impurities below).

Carcinogenicity

Neoplastic potential was assessed in near lifetime oral exaggerated exposure studies in rats and mice. Naloxegol is not a human relevant carcinogen and is not a carcinogen in mice. Naloxegol modulates luteinising hormone (LH) and prolactin (PRL) associated hormone driven, hyperplasia associated neoplastic responses in rats ("non genotoxic" mode of action). Rats are known to be hypersensitive to these types of threshold effects. Accordingly the effects are usually not regarded as human relevant and/or the rat dose response threshold is regarded as being adequately protective of humans.

Chronic near lifetime oral exposure of male rats to extreme supratherapeutic doses of naloxegol results in dose related increased incidence of Leydig cell hyperplasia and a dose related increase in Leydig cell neoplasias that exceed the normal historical background incidence/prevalence at 400 mg/kg/day exposure. The effect is associated with naloxegol-induced LH release from the pituitary, subsequent testosterone surges and is consistent with the known effects of naloxone on LH. Mu opioidergic receptor antagonists are known to increase the release of LH releasing hormone (LHRH) into the hypophyseal portal vessels and LH production in the pituitary in a number of species, including humans. These results do not necessarily imply that naloxegol crosses the intact BBB since LH release by the pituitary is also inhibited by local endogenous opioid receptors in this organ (part of the so-called neuropeptide Y-opioid LHRH axis which involves the preoptic tuberal pathway). However, these results also do not exclude the possibility of CNS effects of naloxegol because opioid receptor components that influence LHRH release are also present in the pre-optic areas of the hypothalamus which are protected by the BBB.

Chronic near lifetime oral exposure of male rats to extreme supratherapeutic doses of naloxegol protects against the development of pituitary adenomas and mammary tumours in rats. Both forms of hormone driven hyperplasia associated neoplastic responses in rats are driven by PRL. Dopamine secreted by tuberoinfundibular dopaminergic neurons (TIDA) in the hypothalamus is the major inhibitory factor controlling prolactin secretion from the anterior pituitary. Endogenous opioid peptides (mainly β endorphin) facilitate PRL secretion by decreasing TIDA dopaminergic neuronal inhibitory tone. Disruption of endogenous β endorphin activity by naloxone increases TIDA dopaminergic inhibitory tone, thus decreasing the stimulus for prolactin production by the anterior pituitary. The TIDA dopaminergic mode of action is possibly relevant to human pituitary adenomas, but the effects on rodent mammary carcinogenesis are unlikely to be human relevant.

[8] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "S2(R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use", 9 November 2011.
[9] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Guidance for Industry S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals", July 1997.

In mice, systemic exposures (plasma AUC) achieved at the high doses were ~39x (males) and 24x (females) the anticipated clinical exposure at the maximum recommended human dose (MRHD). In rats, the exposure (AUC) in both sexes at the high dose was >700x the anticipated clinical exposure. At the NOEL doses for increased tumour incidence in rats, the AUC exposure margins were 46x (male) and >900x (female) the anticipated clinical exposure (notwithstanding the likely lack of relevance of the rat carcinogenicity findings as discussed above).

Reproductive toxicity

Potential naloxegol effects on fertility (rats), embryofoetal (organogenesis) development (rats, rabbits) and pre and postnatal development (rats) were evaluated in oral studies. Naloxegol did not affect fertility in male or female rats at doses up to 1000 mg/kg/day. In the absence of maternotoxicity (manifested as maternal weight loss and reduced food consumption), naloxegol is not an embryofoetal developmental toxicant in rats (NOAEL [maternal]: 750 mg/kg/day correlating with an AUC_{0-24} and Cmax of 479 µg.h/mL and 30.4 µg/mL, respectively; NOAEL [embryofetal] 750 mg/kg/day). At maternotoxic doses (1000 mg/kg/day), maternal naloxegol exposure resulted in an increased incidence of bipartite vertebral centra and anorchism in rats.

In rabbits, sub-maternotoxic to marginally maternotoxic exposure to naloxegol was associated with an increased incidence of fused vertebral arches in foetuses during embryofoetal development (skeletal variation; NOAEL [maternal]: 150 mg/kg/day). The predominant maternotoxic findings were limited reductions in food consumption and weight loss. However the highest maternal dose (450 mg/kg/day) was still consistent with the maximal tolerated dose (that is, < 10% weight loss, no signs of severe toxicity and no maternal mortality).

In rats treated from early gestation (gestation day [GD] 6) to weaning (postnatal day [PND] 20), sub-maternotoxic doses were associated with developmental delay in the F1 male pups manifesting as a > 10% decrease in F1 male body weight gain at study termination without clear evidence of compensatory growth and weight gain in the post-weaning period (NOAEL [maternal]: 250 mg/kg/day maternal). Based on poor quality data, naloxegol concentrates in milk (≈ 3x maternal plasma level) and trans-mammary exposure in rodents was likely to be biologically significant.

Based on the limited human data available and evidence of adverse developmental outcomes in animals that are of uncertain human relevance, the recommended pregnancy category is B3.[10]

[10] Category B3: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans."

Table 9: Relative exposure.

Species	Study	Dose (mg/kg/day)	Mean AUC_{0-24h} (µg·h/mL)†	Exposure ratio#
Rat (SD)	Embryofoetal development (LS-2007-044)	250	206	566.1
		750	479*	1316.2
		1000	599	1646
Rabbit (NZW)	Embryofoetal development (LS-2009-005)	30	3.53	9.7
		150	26.2*	72.0
		450	135	371.0
Human (healthy volunteers)	steady state	25	0.3639	–

= animal:human plasma AUC_{0-24h}
† = At study termination
* = NOAEL

Adequate exposure to the parent drug was achieved in the reproductive and developmental studies. Toxicokinetic monitoring was incorporated into the study designs only for the rat and rabbit embryofoetal development studies (tabulated above). In the fertility study, the highest dose (1000 mg/kg/day) was ≈ 360x the MRHD on a body surface area basis (25 mg/day = 0.5 mg/kg/day in a 50 kg person = 16.5 mg/m^2/day). Based on the AUC exposures achieved in SD rats at 1000 mg/kg/day in the 7 day study (N120, LS-2007-005) and at 500 mg/kg/day in the 4 week study (LS-2007-011, G4754), it is likely that the AUC achieved in the fertility study would have been >1000x the clinical AUC at the MRHD. In the pre/postnatal study, the highest dose (500 mg/kg/day) was ca 180x the MRHD on a body surface area basis (NOAEL 250 mg/kg/day ≈ 90x clinical MRHD). Based on the AUC exposures achieved in the dose ranging study (3270WR), the respective estimated AUC exposures at 500 and 250 mg/kg/day would be ≈ >1000x and >500x the clinical AUC at the MRHD.[11]

In a preliminary study in lactating rats, transfer of naloxegol into milk was very high, with naloxegol concentrating in milk relative to plasma (3x greater than plasma concentration). However, the assay selectivity evaluation failed acceptance criteria due to the extremely low recovery in some samples. Trace levels of naloxegol were detected in milk samples from the control animals (≈ 1000x lower than milk concentrations from low dose animals). No explanation for this finding was provided.

Pregnancy classification

The sponsor has proposed pregnancy Category B1[12] based upon the presence of embryofoetal developmental effects at AUC ratios > 70x at human clinical exposure levels.

[11] AUC at 250 mg/kg/day: 210 µg.h/mL; AUC at 500 mg/kg/day: mean of AUC at 250 mg/kg/day x 2 (420 µg.h/mL) and AUC at 750 mg/kg/day x 2/3 (345 µg.h/mL) = 382.5 µg.h/mL.
[12] Category B1: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage."

The B1 classification is the same as that for naloxone; however, naloxone does not display effects on embryofoetal development at exposures ≥ 1000x human clinical exposure levels.

The assessor recommends pregnancy Category B3 due to: (a) the lack of human relevant data; and (b) the presence of an increased occurrence of foetal damage in animals, the significance of which is considered uncertain in humans.

Local tolerance

There is no evidence of adverse site of first contact effects in the gastrointestinal tract in animals.

Impurities

All non genotoxic impurities and degradants are adequately qualified. Most of the genotoxic impurities are not qualified under published guidelines,[13] although all genotoxic impurities are qualified under ICH M7. The additional risk presented by qualification under ICH M7[14] rather than EMA guidelines[15] is negligible. The qualification of genotoxic impurities and degradants is addressed.

Paediatric use

The safety and effectiveness of Movantik have not been established in paediatric patients.

Nonclinical summary and conclusions

Summary

- The nonclinical section of the dossier is of adequate scope and quality.
- Naloxegol is a μ-opioid receptor antagonist in vitro that did not affect opiate analgesia in a rat model except at high doses. In rats, oral naloxegol reversed morphine-induced small intestinal ileus. The PEGylation of naloxone to produce naloxegol does not affect μ-opioid receptor antagonism and, desirably, reduces κ and δ opioid receptor affinity.
- Naloxegol has a low risk of producing adverse cardiovascular effects. Although in dogs it elicited transient hypotension, reflex tachycardia and PR elongation in safety pharmacology studies (at ≥7.5x clinical Cmax), this was not confirmed in 14 day repeat dose studies at much higher doses, and in vitro cardiovascular assessments were benign. Naloxegol is unlikely to affect gastric emptying or to induce ileus at human clinical exposures. Naloxegol did not trigger opiate-induced physical withdrawal, physical dependence, drug seeking and/or addictive behaviours, analgesia, or overt psychoactive effects in rats. Supratherapeutic doses of naloxegol modified addictive behaviours in rats (partial to complete reversal of the discriminative effects of morphine; NOAEL ≈ the proposed clinical dose).

[13] European Medicines Agency, "Guideline on the limits of genotoxic impurities (EMEA/CHMP/QWP/251344/2006)", 28 June 2006; European Medicines Agency, "Questions and answers on the 'Guideline on the limits of genotoxic impurities' (EMA/CHMP/SWP/431994/2007 Rev. 3)", 23 September 2010.

[14] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk", 23 June 2014.

[15] European Medicines Agency, "Guideline on the limits of genotoxic impurities (EMEA/CHMP/QWP/251344/2006)", 28 June 2006; European Medicines Agency, "Questions and answers on the 'Guideline on the limits of genotoxic impurities' (EMA/CHMP/SWP/431994/2007 Rev. 3)", 23 September 2010.

- Naloxegol oral bioavailability is low and dose dependent (likely due to saturation of enterothelial ABC B1,[16] a potential source of drug-drug interactions). Fasting doubles oral bioavailability. Rats show a species specific sex difference in oral bioavailability; females have lower Tmax (≈2-6x) and higher Cmax and $AUC_{0-\tau}$ (≈ 2x) than males (consistent with sex differences in enterothelial ABC B1 efflux transporters). Oral naloxegol has two compartment plasma elimination kinetics, high clearance and a short β phase t½, which varies with dose implying non 1st order elimination kinetics, particularly at high doses. Enterohepatic cycling may occur in humans with biliary excretion being the major pathway of excretion in rats. Naloxegol has a low affinity for plasma proteins. Repeated daily oral dosing results in plasmatic accumulation in rats (particularly males; species specific effect) with AUC_{0-24} approx. doubling over time. Rat autoradiography showed tissue Tmax higher in females. Elimination of radioactivity was rapid (≤24 h). Naloxegol has an affinity for melanin containing tissues (including uveal tract and skin) as well as liver and kidney and glandular tissues (adrenals, Harderian, pituitary, preputial, salivary and thyroid glands), which do not appear to affect its toxicological properties. Distribution of naloxegol associated radioactivity to the CNS was low (although higher in female than male rodents). Foetal brain exposure is low, but is higher than maternal CNS exposure (with a slower rate of decline). Naloxone PEG≥ 5 conjugates have negligible BBB penetrance.
- Orally administered naloxegol is mostly not absorbed and excreted unchanged in faeces. Absorbed naloxegol undergoes limited CYP3A4/5 (and limited CYP2D6)-mediated O-de-alkylation/oxidation of the PEG chain and/or naloxone C3 O-glucuronidation. In animals, systemic metabolite exposure was ≈ 20x parent drug exposure. The terminal t½ attributable to metabolites was ≈ 2x that of parent. All metabolites found in human samples were detectable in animals; naloxegol glucuronide is a significant metabolite in animals but not humans. Naloxegol is mostly excreted within 48-72 h, and faeco biliary elimination predominates. Under therapeutic conditions, naloxegol is not a CYP inhibitor or inducer. Naloxegol is an ABC B1 efflux transporter substrate but does not inhibit this transporter or OATP1B1, OATP1B3 or BCRP. Inhibition of enterothelial OATP1A2 efflux transporters is a well known cause of drug interactions, but effects on OATP1A2 were not evaluated. Although naloxone inhibits enterothelial OATP1A2, the sponsor claims that an effect of naloxone on OATP1A2 substrates in vivo has not been reported in clinical studies, and that potential naloxegol-OATP1A2 interactions are unlikely.
- Naloxegol has low acute toxicity, and repeated oral exposure is well tolerated. Repeat dosing in rodents was associated with declines in body weight/gain and food intake (likely correlated with delayed gastric emptying). Male mice showed generalized chronic systemic glucocorticoid stress responses characterised by reduced reticulocyte counts in the absence of other overt erythro-dyscrasias (not human relevant). Naloxone is known to attenuate stress induced bone marrow erythrohyperplasia in rodents and reduced circulating reticulocytes are consistent with this type of effect.[17] Other rodent chronic glucocorticoid stress responses (e.g. reduced uterine weight and uterine atrophy) were associated with repeated oral supratherapeutic exposures. High dose naloxegol induces respiratory and olfactory epithelial damage (NOAEL AUC exposure > 70x clinical) and cholecystitis in mice (NOAEL AUC exposure > 250x clinical). Increased serum cholesterol (non-adverse) was consistently observed across species. Repeated oral exposure in dogs resulted in soft stools and/or diarrhoea, with neurotoxicity toxicity observed in the 36 week dog study (NOAEL AUC exposure > 150x clinical).

[16] Naloxegol is an ABC B1 efflux transporter substrate.
[17] Zakharova OI, et al. The participation of opiatergic mechanisms in the regulation of bone marrow hematopoiesis in stress. *Patol Fiziol Eksp Ter.* Nov-Dec;(6): 11-14 (1989).

- Naloxegol (oxalate salt) and its S9 metabolites were not genotoxic in standard in vitro or in vivo assays. Naloxegol is not a murine carcinogen; in rats, naloxegol modulates LH and PRL associated hormonal hyperplasia associated neoplasia (Leydig cell hyperplasia/neoplasia in male rats, not human relevant). Naloxegol is protective against pituitary adenomas and mammary carcinoma in rats, most likely due to reduced PRL production.
- Naloxegol does not affect fertility or embryofoetal development in rats in the absence of maternotoxicity. In rabbits, sub maternotoxic/minimally maternotoxic but supra-therapeutic exposure to naloxegol during organogenesis was associated with an increased incidence of fused vertebral arches in foetuses (relative AUC exposure 370x clinical exposure, ≈ 70x at the NOAEL). A naloxegol-mediated effect on vertebral arch development could not be conclusively excluded. In rats, sub maternotoxic doses through gestation and lactation were associated with developmental delay in the F1 male pups (> 10% decrease in body weight gain compensatory growth post weaning; NOAEL 90x clinical dose). Naloxegol concentrates in milk (≈ 3x maternal plasma level) and trans-mammary exposure in rodents was probably biologically significant.
- Despite its affinity for melanin, naloxegol is unlikely to be a significant photosafety hazard. Because of its affinity for ocular melanin, naloxegol (or its metabolites) may produce retinal effects such as dyschromatopsias. These types of effects are difficult to evaluate in animal studies. There is no nonclinical evidence of ocular toxicity.
- There is no evidence of unacceptable local tolerance relevant to the oral route of exposure.
- All non-genotoxic metabolites, impurities and degradants are toxicologically qualified, and all genotoxic impurities and degradants are qualified under ICH M7.[18]

Conclusions

- There are no nonclinical objections to the registration of Movantik.
- Naloxegol appears to effectively reverse opioid-induced small intestinal ileus in vivo in rats while not reducing opioid analgesia except at supra-therapeutic doses.
- Naloxegol does not trigger opiate-induced physical withdrawal, physical dependence, drug seeking and/or addictive behaviours, overt central μ-receptor mediated psychoactive effects and is not analgesic. At human therapeutic exposure levels, naloxegol induces subtle central effects on addictive behaviours in rats.
- Naloxegol oral bioavailability is low but dose dependent (due to saturation of enterothelial ABC B1 efflux transporters). Oral absorption is rapid and fasting doubles bioavailability. Distribution to brain is minimal. Naloxegol undergoes limited, rapid metabolism mostly by CYP3A4/5. Elimination of systemically absorbed parent drug and metabolites is relatively rapid and predominantly faeco-biliary.
- Naloxegol has low acute (single exposure) toxicity and repeated oral exposure is generally well tolerated.
- Naloxegol is not genotoxic per se but several of its impurities/degradants are, although these have been adequately qualified at the proposed specifications. Naloxegol is not a human-relevant carcinogen.

[18] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk", 23 June 2014.

- A naloxegol mediated effect on vertebral arch development in rabbits at high relative exposures (non maternotoxic to minimally maternotoxic exposures) cannot be categorically excluded, supporting a pregnancy Category of B3. Naloxegol may concentrate in milk in lactating rats, and treatment at a high dose through gestation and lactation delayed male F1 development.
- Naloxegol displays adequate site of first contact tolerance in oral exposure animal studies.
- Because of its affinity for ocular melanin, naloxegol (or its metabolites) may produce retinal effects such as dyschromatopsias, effects which are difficult to evaluate in animal studies. There is no nonclinical evidence of ocular toxicity.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Constipation is a common problem with OIC. The sponsor notes that prescription and over-the-counter laxatives are commonly used to treat OIC in clinical practice but do not specifically target the opioid mediated mechanisms that cause constipation and are not effective in some people.

> *Comment: The actual incidence of OIC for people in Australia is not given. Further, the incidence of OIC for people using concurrently available laxative therapies appropriately is not given. Lastly an estimate of the proportion of constipation in people taking opiates is due to agonism of the mu receptor (and not underlying disease or physical state) would be helpful.*

The physiological effects of opioids are primarily mediated by three major opioid receptor sub-types: μ, κ and δ. Naloxegol is a competitive μ and δ opioid receptor antagonist and a weak partial κ-receptor agonist. Mu (μ) opioid receptors are widely distributed in the CNS and are involved in the perception of pain, and in the myenteric and submucosal plexi of the enteric nervous system where they contribute to peristaltic activity. Thus although the analgesic effects of exogenous opioids rely upon distribution to the CNS, their effect on gut function, one of the reasons the development of OIC, is thought not to be.

> *Comment: There is some evidence that gut function is also controlled by central neural pathways, which would be affected by transport of opiate across the blood brain barrier but not reversed by an antagonist such as a PAMORA that didn't cross. The clinical effect of partial agonism on κ-opioid receptors is not discussed in the clinical submission apart from reference to a rabbit vas deferens assay where naloxegol was shown to have no agonist activity in this assay. The sponsor should discuss the relative contributions of gut opiate to constipation in this population.*

PAMORAs which include naloxegol but also methylnaltrexone, alvimopan and others are a new class of drugs. Naloxegol is PEG naloxol, also known as a PEGylated derivative of naloxone. It is a substrate of the P-gp transporter.

> *Comment: P-gp is important in the transport of many other drugs across the gut wall (and blood brain barrier) and therefore the possibility of drug interactions are high.*

Due to the lack of formal guidance or precedent for defining a clinically relevant difference in OIC response rate for 12 week studies, the sponsor states that the definition of a clinically relevant effect for naloxegol treatment was based on review of literature, on regulatory guidelines available for similar conditions (for example, Irritable Bowel Syndrome),[19] and on consultations with external experts. Based on these factors, the sponsor considered a 10-15% point difference in responder rate, defined by sustained increase in the number of spontaneous bowel movements (SBM) compared with placebo, as a clinically relevant therapeutic gain. In the Camilleri manuscript cited by the sponsor when justifying the choice of endpoint, it is stated that "the bowel function diary has been validated for use in characterising and quantifying constipation symptoms related to opioid use, following guidance from the Food and Drug Administration (FDA) for patient response outcomes (PRO) instruments… the diary has the advantage that it supports the validity of composite PRO end points (SBM, CSBM [complete spontaneous bowel movement]) favoured by regulatory authorities, as well as symptom severity items identified as relevant by patients… In addition, among patients who reported constipation, the number of SBM discriminates between those who reported varying degrees of symptom severity.[20]

> *Comment: the clinical rationale for drug development given by the Sponsor was disappointing. The other factors that contribute to constipation (and are often remediable) whilst on opioids were not discussed. The sponsor has implied that constipation on opioids is due to agonism of the mu receptor, likely to be important but not the sole cause. Also, although the sponsor cites the Camilleri paper as showing that effect of opioid on causing constipation is due to local effects of opioid, on re-reading that article the authors also state "The cause of constipation in opiate users is multi-factorial";[21] for completeness a discussion on the role of central mu-receptor effect on gut function (i.e. role of central neural pathways on gut function) is pivotal to the rationale for developing and using this agent.*

It is difficult to make a decision on the appropriateness of the choice of 10-15% difference in responder rate in the absence of peer reviewed guidelines. It is possible that a greater percentage is more important the lesser number of SBM/week. The PRO instruments appear to have direct clinical relevance and it is unclear why the PRO were not chosen as the primary endpoint in the pivotal clinical studies the expert manuscript quoted (Camilleri et al.)[22] however suggests there is at least some cogniscence (unreferenced) of the link between SBM and PRO.

Guidance

The EU concept paper on the need of a guideline for clinical investigation of medicinal products for the treatment of chronic constipation was reviewed for interpretation of choice of endpoints in this submission.[23]

In addition, sponsor provided and cited literature was reviewed and considered. The sponsor refers to a discussion with the FDA and the Committee for Medicinal Products for Human Use (CHMP) on the studies included in the Phase III program. In this discussion

[19] US Food and Drug Administration, "Guidance for Industry Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment", May 2012.
[20] Camilleri M, et al. Validation of a bowel function diary for assessing opioid-induced constipation. *Am J Gastroenterol.* 106: 497-506 (2011).
[21] Camilleri M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. *Am J Gastroenterol.* 106: 835-842 (2011).
[22] Camilleri M. Opioid-Induced Constipation: Challenges and Therapeutic Opportunities. *Am J Gastroenterol.* 106: 835-842 (2011).
[23] European Medicines Agency, "Concept paper on the need of a guideline for clinical investigation of medicinal products for the treatment of chronic constipation (EMA/CHMP/462198/2012)", 18 October 2012.

there was discussion on the definition of 'responders', the stool screen and appropriateness of the use of US data in a EU population.

Responder

A responder to study drug during Weeks 1 to 12 was defined as a patient with at least 3 SBMs/week and at least a 1 SBM/week increase over baseline for at least 9 out of the 12 treatment weeks and 3 out of the last 4 treatment weeks during the double blind treatment period.

> *Comment: whilst noting the advice was from authoritative bodies, the clinical relevance of, for example, 4 SBM/week for ¾ weeks as opposed to 3 SBM/week is unclear in terms of the population in this indication especially in cancer or in the elderly with non-cancer pain, that is, the clinical relevance of Quality of Life (QoL), reduced hospital admissions and other side effects of constipation stated by the Sponsor could be highlighted.*

Change of 4 week to 12 week primary endpoint

The original 4 week primary endpoint in the confirmatory studies was changed in a protocol amendment approximately 11 months before unblinding to a response evaluated over the entire 12 week study duration. This agreement also included using a multiple testing procedure (MTP) to control the overall type-I error across the primary and key secondary endpoints, for comparisons between the two naloxegol doses with placebo.

Stool symptom screener

A qualitative research study examined the stool symptom screener questions included in the Baseline Laxative Response Status Questionnaire (BLRSQ), used to define the patient's baseline laxative response status. This was evaluated.

> *Comment: The sponsor notes that reference was been made to EMA and US for cancer indications (Refer to EMA Final Advice 2010 April, 2011 July, as well as 2013 April) however the evaluator was unable to locate this discussion. Specific considerations were said to be endorsed during the regulatory consultations regarding the design and conduct of studies with naloxegol in the cancer pain population, which are not specifically listed above (the sponsor is seeking an indication that enables use of naloxegol in the cancer pain population). It is stated by the sponsor that the special warnings and precautions section of the Prescribing Information will include applicable restrictions, which are anticipated to be amended as data become available in this population. It is noted that the proposed PI states "there is very limited clinical experience with the use of Movantik in OIC patients with cancer-related pain. Therefore caution should be used when prescribing Movantik to such patients".*

Contents of the clinical dossier

The clinical dossier documented biopharmaceutic, clinical pharmacology and clinical trial data to support the application.

The naloxegol biopharmaceutic and clinical pharmacology program included in this submission included 14 completed Phase I studies in 438 volunteers including 24 subjects with mild hepatic impairment and 16 subjects with renal impairment.

The Phase II development programme constituted a single Phase IIb study with 208 randomised patients, guided the choice of the 25 mg but not the 12.5 mg) naloxegol doses used in the Phase III development program.

The Phase III development program included in this submission includes a total of five studies: 2 identical placebo controlled, double blind, 12 week Phase III confirmatory

studies (Studies 04 and 05), a double blind, 12 week safety extension study (Study 07) of Study 04, a randomised, open label, 52 week parallel group long term safety study (Study 08), and a placebo controlled double blind study in patients with cancer-related pain and OIC (Study 06).

There were also pooled data for safety, pharmacokinetic (pharmacodynamics [PD] and pharmacokinetics [PK]), exposure outcome modelling and analysis.

Phase I studies (biopharmaceutic and clinical pharmacology)

- 08-PNL-04: "An Open-Label, Randomised, Single-Dose, 2-Treatment, 2-Period, Crossover Study in Healthy Female and Male Subjects to Evaluate NKTR-118 Tablet Bioavailability Relative to NKTR-118 Solution"
- D3820C00025: "A Phase I, open-label, randomised, balanced, single-dose, 2-part study to assess the relative bioavailability of NKTR-118 in 3 formulations under fasted (3-way cross-over) and fed (2-way cross-over) conditions in male and non-fertile female volunteers"
- D3820C00018: "A Phase I, randomised, open-label, 3-way cross-over study in healthy volunteers to demonstrate the bioequivalence of the naloxegol 25 mg commercial and phase III formulations and to assess the effect of food administration on the pharmacokinetics of the commercial formulation"

Pharmacokinetics studies

- 05-IN-OX001: "A double-blind, placebo-controlled, dose escalation crossover study to evaluate antagonism of single oral doses of PEG7-Naloxol (naloxegol) on peripheral and central effects of morphine in healthy male volunteers"
- 07-IN-NX002: "A Phase I, double-blind, randomised, placebo-controlled, multiple-dose study to evaluate the safety, tolerability and pharmacokinetics of escalating oral doses of NKTR-118 (naloxegol) in healthy male and female volunteers"

  (Note this study used NKT-10018 which is the same product as NKTR-118).
- D3820C00001: "A Phase I, open-label, single-centre study to assess absorption, distribution, metabolism and excretion after [14C]-labelled oral administration of NKTR-118 (naloxegol) to healthy male volunteers"

Studies examining the effect of intrinsic factors

- D3820C00009: "An open-label, parallel-group, phase I study to compare the pharmacokinetics of naloxegol following a single oral dose in subjects with renal impairment and subjects with normal renal function"

Naloxegol clinical pharmacology studies

- D3820C00010: "An open-label, single-centre study to assess the pharmacokinetics of NKTR-118 (naloxegol) in patients with impaired hepatic function and healthy volunteers with normal hepatic function following administration of a single dose of 25 mg naloxegol"
- D3820C00020: "A Phase I, randomised, double-blind, placebo-controlled study to assess the safety, tolerability and pharmacokinetics of NKTR-118 (naloxegol) following single and multiple ascending oral dose administration in healthy young and elderly Japanese volunteers, and an open, randomised, crossover study to investigate the effect of food on the pharmacokinetics after single oral doses of naloxegol in healthy male young Japanese volunteers"

- D3820C00011: "A randomised, 2-part, crossover, single centre study to evaluate the effect of quinidine on the pharmacokinetics of NKTR-118 (naloxegol) and the concomitant effect of quinidine and naloxegol on morphine-induced miosis"
- D3820C00012: "An open-label, 1-sequence, 3-period, 3-treatment, crossover study to assess the effects of ketoconazole on the pharmacokinetics of NKTR-118 (naloxegol) in healthy subjects"
- D3820C00015: "An open-label, fixed-sequence, 3-period, 3-treatment, crossover study to assess the effects of rifampin on the pharmacokinetics of naloxegol in healthy subjects"
- D3820C00032: "An open-label, sequential, 3-period study to assess the effects of diltiazem on the pharmacokinetics of naloxegol in healthy subjects"

Pharmacodynamics studies

- D3820C00014: "A single centre, randomised, double-blinded, placebo- controlled, open-label, positive-controlled, 4-way cross-over study to assess the effect of a single oral dose naloxegol administration on the QT-interval compared to placebo, using AVELOX (moxifloxacin) as a positive control, in healthy male volunteers"

Phase II, safety and efficacy studies

- 07-IN-NX003 (Phase IIb study): "A Phase II, double-blind, randomised, placebo-controlled, multiple-dose, dose escalation study to evaluate the efficacy, safety and tolerability of naloxegol in patients with opioid-induced constipation"

Phase III studies

- D3820C00004: "A randomised, double-blind, placebo-controlled study to assess the efficacy and safety of naloxegol in patients with non-cancer related pain and opioid-induced constipation"
- D3820C00005: "A randomised, double-blind, placebo-controlled study to assess the efficacy and safety of naloxegol in patients with non-cancer related pain and opioid-induced constipation"
- D3820C00006: "A randomised, double-blind, placebo-controlled study to assess the efficacy and safety of naloxegol in relieving opioid- induced constipation in patients with cancer-related pain"
- D3820C00007: "A randomised, double-blind, placebo-controlled 12-week extension study to assess the safety and tolerability of naloxegol in patients with non-cancer related pain and opioid- induced constipation"
- D3820C00008: "An open-label 52-week study to assess the long-term safety of naloxegol in opioid-induced constipation (OIC) in patients with non-cancer related pain"

Paediatric data

The sponsor submitted an application for a Paediatric Investigation Plan (PIP) including a deferral and a waiver for naloxegol for the treatment of OIC in August 2011 (PIP Procedure No. EMEA-001146-PIP01-11). The Paediatric Committee's (PDCO) formal opinion was adopted by the EMA in August 2012. A deferral was agreed regarding the initiation and completion of the naloxegol paediatric study until a juvenile rat toxicology study is complete and PK, safety and efficacy are evaluated in the adult population. An age appropriate formulation will be developed. A waiver was granted for studies in children less than 6 months because of potential incomplete development of the blood brain barrier in this age group.

Good clinical practice

The sponsor standard operating procedures, quality control measures, and audit programs provide reassurance that the clinical study program was carried out in accordance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines, as documented by the International Conference on Harmonisation (ICH), FDA, and EMA. Up-to-date GMP documentation was provided for the three sites (US, Belgium and Sweden).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 10 shows the studies relating to each PK topic.

Table 10: Submitted PK studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	D3820C00025
		05-IN-OX001
		D3820C00001
	- Multi-dose	08-PNL-04
		D3820C00018
		07-IN-NX002
		D3820C00020
	Bioequivalence - Single dose	
	- Multi-dose	08-PNL-04
		D3820C00025
		D3820C00018
	Food effect	D3820C00025 D3820C00018 D3820C00020
PK in special populations	Target population - Single dose	
	- Multi-dose	07-IN-NX003 (Phase IIb study)
	Hepatic impairment	D3820C00010
	Renal impairment	D3820C00009
PK interactions	Quinidine Ketaconazole Rifampin Diltiazem Effect on QT	D3820C00011 D3820C00012 D3820C00015 D3820C00032 D3820C00014

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

It should be noted that the conclusions are based on the evaluator's review of each PK study report.

The appendices summarise all of the PK data in pooled form with mathematical extrapolations. This data was helpful to check the actual clinical data and to concur with the modelling.

There were a large number of PK studies. Most of this was in healthy volunteers. Data from groups most likely to be using this therapy was lacking. This was driven by a lack of consideration of the population in Australia most likely to use this therapy, for example, who is currently using chronic opioids? Which groups of these tend to have OIC? What combination of therapies are these people on, as in practice this therapy will be added on to their current medication list? Some of the variables did not reach significance as a covariate in the PK modelling however numbers were very small and there was sparse data for some groups.

Specifically in Australia, these groups of patients not well represented in the clinical studies and in whom there may be significant issues translating the data are:

- the elderly (non-cancer chronic musculoskeletal pain inter alia). A small number (10%) of patients > 65 years were included, and exposure was noted to increases with age. In the Phase I study D3820C00020, following multiple dose administration of 12.5 to 100 mg NKTR-118 the steady state exposure to NKTR-118 at 25 mg was higher in the elderly than the young subjects, associated with slightly higher accumulation ratio.
- those with cancer
- Body Mass Index (BMI) >30
- Ethnic groups other than white
- Children/adolescents
- Renal impairment: CrCl <60, < 30, <15 ml/min as D3820C00009 did show an increase in AUC with increasing dose in renal impairment.
- Chronic dosing (> more than 8 days), that is, in Study 07-IN-NX002: a multiple dosing PK study, overall, plasma NKTR-118 concentration-time profiles on Day 8 were between 33% and over 100% higher than on Day 1. Drug was taken bis in die (BID; twice daily).
- D3820C00010. In this study, the results suggest that after a single dose, exposure of NKTR-118 25 mg does not seem to be dependent on the severity of hepatic impairment (based on their Child-Pugh scores) in patients with mild and moderate hepatic impairment.
- Recommendations to use a half dose for some population groups are not supported by the evidence.

Pharmacodynamics

Studies providing PD data

Table 11 shows the studies relating to each PD topic.

Table 11: Submitted PD studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on OIC	07-IN-NX003
Secondary Pharmacology	Effect on antagonism of single oral doses of PEG7-Naloxol on peripheral and central effects of morphine in healthy male volunteers	05-IN-OX001
	The concomitant effect of quinidine and naloxegol on morphine-induced miosis	D3820C00011
	Effect on QT interval	D3820C00014
Gender other genetic and Age-Related Differences in PD Response	Effect of gender/age	Not undertaken but examined in the context of other studies
Population PD and PK-PD analyses	Healthy subjects	Pooled data
	Target population	Pooled data

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Overall, the PD data is weak for this submission. Information on the effect of gender, BMI, age and race on PD response is necessary due to the population likely to be using this.

Dosage selection for the pivotal studies

The doses of naloxegol used in the Phase III program were 12.5 and 25 mg once daily. The naloxegol 25 mg once dose was selected based on efficacy and tolerability demonstrated in the 4 week Phase IIb study (Study 07-IN-NX-003).

That study was a 4 week Phase II dose finding study (5, 25, 50 and 100 mg). The sponsor made the decision to perform a preliminary analysis of the primary endpoint to determine if further dose cohorts were required to define the appropriate Phase III dose at each stage. As a result of this analysis, due to safety issues with the 50 mg dose, a decision was made to end the study after completion of the third cohort. The 25 mg once daily dose was identified as a safe and tolerable dose appropriate for Phase III testing.

The 12.5 mg once daily dose was included in the Phase III program, even though the efficacy data in the Phase II study above was inconsistent in terms of efficacy for all of the parameters and the 5 mg dose showed no efficacy (there was no 12.5 mg dose). Specifically, although the primary endpoint was significant for an average extra 1.6 SBM in the first week compared to placebo in the 25 mg group, P = 0.0020), the secondary endpoint of the mean change in SBMs/week from baseline during Weeks 2, 3, and 4 for both Cohorts 1 and 2 (5 mg and 25 mg) were not statistically significant.

The dose selection was supported by pharmacometric modelling.

Although patients were required to stop their prior laxative regimen at study entry, rescue bisacodyl use was allowed during the studies.

> *Comment: the evidence for the choice of the 12.5 mg dose in the Phase III studies is weak.*

Efficacy

Studies providing efficacy data

Clinical evidence for the efficacy of naloxegol is primarily derived Studies 04 and 05: multinational multicentre, double blind, randomised, placebo controlled, parallel group studies of 2 doses of naloxegol (12.5 mg and 25 mg once daily) and placebo, and a placebo controlled, double blind study in patients with cancer related pain and OIC (Study 06).

A Phase IIb study (07-IN-NX-003) was also included in the Efficacy section.

Evaluator's conclusions on efficacy

Overall, there was an increase in the primary endpoint SBM/week of 1-2 on average in the 25 mg group in the pivotal studies. Efficacy was also seen in the Phase II study where the dose of 50 mg was studied.

However, there are some important caveats to make regarding the interpretation of the statistical significance of the primary endpoints. The fact that there were more subjects in the NKTR-118 25 mg group that discontinued treatment and that had adverse events (AEs) than placebo will be covered in the Safety section.

Demographics

Firstly, most subjects in the efficacy studies were from the US and were Caucasian. In the pivotal studies, approximately half of the patients had a BMI ≥30 kg/m^2. The relevance of this to the Australian population and to the cancer population specifically is unclear.

Relationship of statistical response to clinical outcome

The clinical significance (in terms of patient benefit) of the statistically significantly increased number who responded to therapy compared to placebo (increase of at least one SBM per week) was not explicit. There was an increase in mean SBMs per week of nearly one extra SBM in the NKTR-118 25 mg and half in the 12.5 mg groups compared with placebo; 4.4 SBMs per week in the NKTR-118 25 mg group compared with 3.9 and 3.4 SBMs per week in the NKTR-118 12.5 mg and placebo groups, respectively. These small fractional increases of SBM or fractions of days with a CSBM are not discussed.

Relationship of change in individual OIC symptoms to clinical status

In Study 04, stool consistency measurement, over Weeks 1 to 12, statistically significant increases are seen only with only in the 25 mg group and in Bristol Stool Scale (BSS) ratings compared with placebo of only 0.18 ($p = 0.042$). The significance of a 0.18 change in a 7-point scale is not clear. The 25 mg group showed a statistically significant increase in percent number of days with a CSBM/week compared with placebo of 8.59% in the 04 and 11.76% in the Study 05 group. The clinical significance of an extra 8-11% of days per week with a CSBM was not clear.

Relationship of change in individual OIC symptoms clinical status to responder rate (primary outcome)

In the patient relevant endpoints measured by the Patient Assessment of Constipation Symptom Questionnaire (PAC-SYM) and the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL), there were no differences between placebo and either of

the doses of nalexegol in the 04 Study apart from the rectal domain of the PAC-SYM. Improvements on the rectal and stool domain were seen in Study 05 in the 25 mg dose and showed a statistical improvement of 0.5 points on the QoL score, the clinical relevance of this was not clear, nor was the relationship of response (and increase of 1 or more SBM/week) to the QoL.

Concerns

- Concerns relating to lack of OIC data in the cancer population: patients with cancer were excluded from the pivotal trial and the 06 cancer OIC study was closed with only 14 subjects.
- Concerns regarding the choice of dose for pivotal study: the choice of 25 mg for the pivotal study is clear but not the 12.5 mg dose. This correlates with the 12.5 mg dose having poor clinical efficacy.
- Choice of primary endpoint: PRO are likely to be very valid in this disease however it is not clear why, in the absence of a clear definition of what a clinically relevant increase in SBM is (nor whether it is change in stool type versus frequency), that the PRO were not used as primary endpoints.
- Efficacy is subpopulation such as elderly (only 2% older than 75 years in the pivotal study and AUC in the elderly increased), patients with moderate-severe renal impairment (dialysis population and PK are different to patients with CrCl between 15 and 30 ml/min). There is no evidence in the cancer population or in children.
- There is no long term efficacy data greater than 12 weeks which is problematic as the condition for which the opiate is prescribed (which can contribute to the constipation) is a long term condition.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- The Phase II Study 07-IN-NX-003
- The two Phase III efficacy and safety studies (04 and 05)
- A 12 week double blind safety extension study (Study 07- D3820C00007) of Study 04
- A randomised 52 week open label parallel group long term safety study (Study 08 - D3820C00008)
- A study in OIC in Cancer (Study 07)
- Phase I and PK studies

Patient exposure

Duration of exposure for pivotal Studies 04 and 05 are shown in Tables 12 and 13.

Table 12: Pivotal Study 04 – Duration of Exposure.

	Placebo (N = 213)	NKTR-118 12.5 mg (N = 211)	NKTR-118 25 mg (N = 214)
Duration of exposure (days)			
n	213	211	214
Mean	77.5	77.4	74.3
SD	20.75	21.58	25.21
Median	85.0	85.0	85.0
Min	2	4	1
Max	95	113	101
Total patient exposure [a]	16510	16323	15895

Table 13: Pivotal Study 05 – Duration of Exposure.

	Placebo (N=231)	NKTR-118 12.5 mg (N=230)	NKTR-118 25 mg (N=232)
Duration of exposure (days)			
n	231	230	232
Mean	76.1	75.9	72.4
SD	22.68	22.86	27.24
Median	85.0	85.0	85.0
Min	1	1	1
Max	98	112	104
Total patient exposure [a]	17579	17456	16801

Safety issues with the potential for major regulatory impact

There are potential issues with safety, especially when used outside of the non cancer population or healthy populations studied in these trials. Pharmacovigilance should be undertaken if the product has a favourable decision.

These include GI side effects and bowel perforation (latter not seen in the pivotal studies), hypotension, increase in pain, hyperhidrosis and other symptoms of changes in the autonomic nervous system.

Populations at risk are the elderly, cancer patients and those with organ dysfunction.

Opioid withdrawal was reported in the pivotal clinical study (Study 04).

Liver toxicity

There were two cases of elevation in transaminases in the pivotal studies. Although not meeting criteria for 'Hy's law', vigilance and monitoring should occur, specifically in a chronic pain setting where other medications are commonly co-ingested and over a period of time.

Haematological toxicity

Nil concern from the trial data submitted.

Serious skin reactions

Nil concern from the trial data submitted.

Cardiovascular safety

Nil concern from the trial data submitted.

Unwanted immunological events

Nil concern from the trial data submitted.

Post marketing data

Nil

Evaluator's conclusions on safety

It is noted that in both of the extension studies, all patients were from the US as were a large majority of people in the pivotal studies. The relationship of that population to disease incidence and management in comparison to Australia was not made. The relationship of the demographics and relationship to likely population in Australia was not made.

Overall, the investigational product (IP) showed increased adverse events (AEs) compared to placebo, in a dose-response relationship. Most AEs were gastrointestinal (GI) and some were judged as severe in intensity.

In the Phase II study, in both the 5 mg and 25 mg group treatment emergent adverse event (TEAE) rate was mildly increased, and in the 50 mg group, 85% of patients reported TEAEs as compared to 56% in the placebo arm. Sixteen patients in Cohort 1 (5 mg), 16 patients in Cohort 2 (25 mg) and 23 patients in Cohort 3 (50 mg) experienced at least 1 TEAE that was assessed as being causally related to the study drug, the majority of which included diarrhoea, abdominal pain and nausea. However the most frequent study drug related Grade 3/4 TEAE reported across all 3 dose cohorts was abdominal pain.

Following review of 8 AEs of special interest in this study, the Dose Evaluation Safety Committee (DESC) recommended against dose escalation to 100 mg due to GI safety concerns.

In extension Study 07, more AEs were reported in the 25 compared to the 12.5 mg and placebo groups.

The most common TEAEs in the NKTR-118 treatment groups were arthralgia and diarrhoea, which occurred at a higher frequency in the NKTR-118 treatment groups compared with placebo.

The pivotal studies overall showed that more patients in the NKTR-118 25 mg group had at least 1 AE compared with the NKTR-118 12.5 mg and placebo groups.

In both pivotal studies the most common TEAEs among patients in the NKTR-118 treatment groups (abdominal pain, diarrhoea, and nausea) were from the GI System Organ Class (SOC), and occurred most frequently in the NKTR-118 25 mg treatment group. The proportion of patients with diagnostic adverse events (DAEs) and common GI AEs (abdominal pain, diarrhoea) was also higher in the 25 mg dose group of NKTR-118 compared with both placebo and the 12.5 mg dose group. The most common DAEs were GI AEs.

A higher rate of severe GI AEs was also observed in the NKTR-118 25 mg group compared with the 12.5 mg and placebo treatment groups.

A new AE of hyperhidrosis was reported during the treatment period. In the 04 Study, six of the 9 events began on Day 1 of treatment. One event was assessed as severe in intensity and resulted in study discontinuation, and 1 other moderate event resulted in study discontinuation. Hyperhidrosis was reported more commonly in the 25 mg compared to 12.5 mg groups

The pivotal Study 04 reported three episodes of significant withdrawal (measured by COWS) coded to the MedDRA term of drug withdrawal syndrome. In Study 05, withdrawal symptoms were also reported.

More patients in the NKTR-118 25 mg treatment group had the AE of drug withdrawal reported compared with the other treatment groups (4 in the NKTR-118 25 mg, 1 in the NKTR-118 12.5 mg and none in the placebo group).

One patient did develop transaminitis while on the IP. This requires pharmacovigilance. Small electrocardiogram (ECG) changes were reported which, while being of uncertain significance, require pharmacovigilance.

First round benefit-risk assessment

First round assessment of benefits

The benefits of naloxegol in the proposed usage are:

- In non-cancer patients with OIC, a statistically significant increase in responder rate over placebo (increase by 1 or more SBM/week)

First round assessment of risks

The risks of naloxegol in the proposed usage are:

- Minimal effect on symptoms and quality of life.
- No clinical data in the cancer population
- Paucity of data in the elderly and in racial groups represented in Australia (who may have different dietary or genetic P450 and P-gp expression).
- Non-morphine effects on constipation not addressed
- Significant GI side effects
- Significant inter and intra patient PK variability
- Withdrawal effects of opioids
- Lack of real clinical data in patients with severe renal or liver disease
- Significant changes in exposure when taken concurrently with P450CYP 3A4 inducers or inhibitors or P-gp inhibitors (including food)

First round assessment of benefit-risk balance

The benefit-risk balance of naloxegol is unfavourable given the proposed usage, but could become favourable if the changes recommended are adopted.

Specifically, if the indication was changed to use in non-cancer pain only in patients and for whom an extra SBM/week correlate with symptom improvement. Subjects should unresponsive to other currently available therapies. The 25 mg only dose should be available.

First round recommendation regarding authorisation

Rejection of the submission due to the following major reasons:

- Rationale for the therapy in Australia not given, particularly the difference in the cancer and non cancer populations
- Clinical relationship of increase in SBM or 1 or more per week is not clear.
- Lack of relationship between increase in SBM or 1 or more per week and symptoms.

- Side effect profile including risk of withdrawal, compared to placebo, prominent.

There are other factors which are highlighted in the Questions below which could be addressed and if so may not be reasons for rejection.

Clinical questions

- Post marketing safety data was not provided. Is it available?
- The actual incidence of OIC for people in Australia is not given. Further, the incidence for people using current therapies appropriately is not given. Currently, clinical practice appears to be to start patients on coloxyl and senna and lactulose when opioids are started. Some patients do get constipated, sometimes related to dehydration of another factor. When underlying contributors have been addressed, macrogol is available. Some patients cannot tolerate macrogol, and then may have access to other oral agents or enemas. Can the sponsor describe the place in therapy in Australia? The sponsor should discuss the relative contributions of gut opiate to constipation in the cancer and non-cancer populations.
- Patients who don't respond to these current therapies may have a mechanical obstruction or pseudoileus. Can the sponsor provide number of patients that are likely to be needing treatment in Australia?
- Can the sponsor discuss why the naloxegol was not compared to or extrapolated from standard therapy in Australia?
- Regarding the definition of responders (noting the lack of current CHMP Guidance), while noting the advice was from authoritative bodies, the clinical relevance of, for example, 4 SBM/week for 3 out of 4 weeks as opposed to 3 SBM/week is unclear. It is possibly more unclear in the cancer population on opiates who are often more concerned about symptoms and QoL, that is, reduced hospital admissions than number of SBMs/week.
- It is noted that applications were submitted in Canada and Switzerland in 2013. Is there any follow-up for those applications?

Second round evaluation

Minimal effect on symptoms and QoL

Sponsor response

AstraZeneca's position is that the therapeutic benefit Movantik 25 mg offers is clinically meaningful for patients. It is demonstrated via the primary responder endpoint, which represents a sustained improvement in SBM frequency versus placebo, and supported by all multiplicity protected secondary endpoints, other secondary endpoints that are important for patients, and the analysis of response incorporating symptom data. Overall, the studies were not powered to assess for significant differences between Movantik and placebo for quality of life parameters. Patients suffering chronic OIC are likely to notice and value even shorter periods of lesser improvements. The risks of Movantik recorded in the clinical programme notably are most commonly reversible upon drug discontinuation, not serious, and unlikely to result in permanent sequelae.

These consistent improvements were seen despite a substantial placebo response.

Evaluator response

The evaluator notes the study was not powered to examine improvements in the quality of life. However it appears the main reason to treat this condition, which as the Sponsor notes causes significant effects on quality of life, is improvement in quality of life. The placebo effect, which results in no difference compared to naloxegol for many of the endpoints, is noted. In distinction to the symptomatic nature of this problem, with effects on QoL, the clinical relevance of the primary endpoint of one extra SBM per week for 3 out of 4 is not made. That is, it is not clear if the three extra bowel motions per month improves QOL in the population who had a benefit.

No clinical data in the cancer population

Sponsor response

See the responses in the following sections of this document.

Evaluator response

This information in following sections does not provide clinical data requested. It hypothesises that the benefit and toxicity is likely to be the same as non cancer OIC.

Paucity of data in the elderly

Sponsor response

While there is a small effect of age on the PK of naloxegol (approximately 0.7% increase in AUC for every year increase in the age range studied [18 to 78 years of age]), the magnitude of this change in unlikely to be clinically meaningful. Therefore, no dose adjustment is recommended based on age. This recommendation is supported by clinical findings: Movantik was generally safe and well tolerated in patients ≥65 years of age in both the 12 week pool and after longer exposure. The safety profile in these elderly patients is similar to that seen in younger patients with regard to frequency and type of AEs as well as changes in vital signs, ECGs, and clinical laboratory parameters.

Evaluator response

It is unclear where the 0.7% per year comes from as the table shows there were no patients over 65 in any of the PD or biopharmaceutical studies. There were only 13 people in the 65-74 group and 5 in the 75-84 and 0 over 85s only in the PK studies, and in the efficacy/safety studies, 207 were in the 65-74, 40 in the 65-74 and nil over 80. There is thus minimal data in the over 65 age group.[24]

AstraZeneca proposes the following language for inclusion in the *PHARMACOLOGY, Pharmacokinetics, Special populations* section of the proposed PI.

> *Age and gender*
>
> *Patients over 65 years of age have been well represented in the Phase III studies. There is a small effect of age on the pharmacokinetics of naloxegol (approximately 0.7% increase in AUC for every year increase in the age range evaluated in the clinical studies [18 to 78 years of age]). Clinical studies of Movantik did not include sufficient numbers of patients aged 75 years or over to determine whether they respond differently than younger patients; however, the magnitude of the small change in PK observed with age is unlikely to be clinically meaningful. No dose adjustment is recommended for the elderly patients as this age group has been well represented in the phase III trials.*

[24] It is acknowledged that this issue was later resolved.

There is no gender effect on the pharmacokinetics of naloxegol.

The evaluator believes this is misleading. Rather it is recommended to state "patients over 65 years of age have been poorly represented in the Phase II and III studies. There were no patients over 65 in any of the PD or the biopharmaceutical studies, 13 in the 65-74 age groups, 5 only in the 75-84 group and 0 over 85s only in the PK studies, and in the efficacy/safety studies 207 in the 65-74, 40 in the 65-74 and nil over 80. This drug has thus not been well studied in the 65-84 age group and care should be taken if using in this population. The drug has not been studied in any form in the population over 85 and is not recommended".

Paucity of data in racial groups represented in Australia (who may have different dietary or genetic P450 and P-gp expression)

Sponsor response

Polymorphism data on P-gp are controversial and genotype has been shown to have little impact on cytochrome P450 3A (CYP3A4)/5 activities. Consequently, the effects of the polymorphism of CYP3A4 and P-gp are usually not investigated in most drug development programmes. In addition, there are no known issues with genotype or single nucleotide polymorphisms for CYP3A4 or P-gp; therefore, it is expected that exposure and the pattern of safety and efficacy in the Australian population will be similar to what has been studied in North America and Europe. In alignment with the findings of the Risk Management Plan (RMP) reviewer, AstraZeneca's position is that the results of the clinical studies are expected to be broadly applicable to the Australian population.

Evaluator response

The evaluator notes that there is little evidence to assume the patient population using the drug in Australia will be broadly similar to those in the clinical trials. For example, the prevalence of Black Americans in the US and the large East Asian, Indigenous and Southern Asian populations in Australia. Dietary issues affect P450 and P-gp expression as well as racial differences; this is thus very likely to have effects on the PK parameters and drug concentrations.

It is normal practice for physicians to monitor the response of their patients to the dose prescribed, and it is anticipated that patients will be monitored as per standard of care. AstraZeneca acknowledges that data on racial groups in Australia are limited and proposes to include analyses of relevant cases, which will be provided in the annual Periodic Benefit-Risk Evaluation Report (PBRER).

It is important to evaluate this in the PBRER. In addition it should state in the PI that there is a paucity of data in racial groups represented in Australia thus care should be taken with additional efficacy and toxicity monitoring.

Non-morphine effects on constipation not addressed

Sponsor response

AstraZeneca acknowledges that the pathophysiology of OIC is multifactorial; however, the extent of clinical efficacy demonstrated with Movantik and other peripherally acting μ-opioid receptor antagonists (PAMORAs) suggests that inhibition of opioid signalling in the periphery only is sufficient to manage OIC. While there may be a small contribution to constipation from central opioid effects, it is pivotal to exclude inhibition of signalling in/to the brain as not to interfere with pain management and not to cause opioid withdrawal. Clinical data demonstrate relief from OIC with Movantik use, while not interfering with analgesia or causing opioid withdrawal to any significant degree.

Evaluator response

This response acknowledging the difficulties in blocking peripheral versus central opioid effects and the complexity of constipation in people using chronic opioids is noted.

Significant GI side effects

Sponsor response

GI AEs are not unexpected with Movantik, given its pharmacologic and physiologic effects (reversal of impaired GI motility and decreased intestinal fluid absorption). The incidence of AEs of abdominal pain and diarrhoea was dose-ordered; most of these events began within the first 7 days of receiving Movantik, and the majority of the events resolved while the patients were on study treatment. Clinically important GI AEs (that is, serious GI AEs, discontinuations due to GI AEs, and GI AEs of severe intensity for the preferred terms of abdominal pain, abdominal pain upper, abdominal pain lower, diarrhoea, nausea, vomiting, and flatulence) are an identified risk associated with Movantik. GI perforation, a potential risk associated with Movantik, was not observed in the development program.

Evaluator response

These clinically significant GI AEs are noted in the clinical evaluation report.

Significant inter and intra patient PK variability

Sponsor response

Inter subject PK variability was calculated as approximately 50% in a Phase I bioequivalence study using data from the proposed commercial tablet administered under fasting conditions to normal healthy volunteers. This variability is lower than the inter subject variability reported for statins.

Evaluator response

There is now tens of thousands of patients and patient years data with statins. It is difficult to see how the comparison of a significant pharmacological problem to another drug in a different drug class overrides the acknowledgement and management of the issue with this drug.

No estimates of intra subject PK variability were performed in volunteers or patients. No analyses of inter and intra patient PK variability were performed in the Phase III studies, as PK data were collected using sparse sampling techniques

Sponsor response

AstraZeneca acknowledges that data on exposure in OIC patients in Australia are minimal (n = 1, Study 04) and proposes to include analyses of relevant cases, which will be provided in the annual PBRER.

Evaluator response

This is helpful but unclear how this would be undertaken – would the sponsor be proposing to measure PK at steady state in patients as part of a Phase IV study?

Withdrawal effects of opioids

Sponsor response

Naloxegol, a peripherally acting opioid antagonist with limited CNS penetrance, would not be expected to produce signs of interference with the central analgesic effects of opioids. Opioid withdrawal syndrome was uncommon in the clinical trial program, was generally

not severe or serious, and did not cause discontinuation. AstraZeneca agrees that this is, nonetheless, an identified risk and proposes the following language for inclusion in the PRECAUTIONS section of the proposed PI, which is in alignment with the European Summary of Product Characteristics (SmPC).

> *Opioid withdrawal syndrome*
>
> *Cases of opioid withdrawal syndrome have been reported in the Movantik clinical programme (DSM-5). Opioid withdrawal syndrome is a cluster of three or more of the following signs or symptoms: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhoea, pupillary dilation, piloerection or sweating, diarrhoea, yawning, fever, or insomnia. Opioid withdrawal syndrome typically develops within minutes to several days following administration of an opioid antagonist. If opioid withdrawal syndrome is suspected the patient should discontinue Movantik and contact their physician.*

Evaluator response

This is appropriate, however as it is possible for inhibition of P-gp in the brain to cause transport into the CNS, the line

> *Naloxegol, a peripherally acting opioid antagonist with limited CNS penetrance, would not be expected to produce signs of interference with the central analgesic effects of opioids*

should be rewritten as

> *Naloxegol is a peripherally acting opioid antagonist. In the usual clinical situation limited CNS penetrance occurs, thus it would not be expected to produce signs of interference with the central analgesic effects of opioids. However if the blood-brain barrier is disturbed of there is inhibition of the transport P-gp, signs of central analgesic antagonism is likely.*

Lack of real clinical data in patients with severe renal or liver disease

Sponsor response

AstraZeneca acknowledges that clinical data on OIC patients with severe renal or liver disease are limited and proposes to include analyses of relevant cases, which will be provided in the annual PBRER.

A brief summary of the available data is provided below:

Overall, in severe renal impaired subjects, AUC and Cmax of naloxegol increased by 117% and 84%, respectively, compared to patients with normal renal function (Study D3820C00009). However, in 2 out of 8 subjects (in both the moderate and severe renal impairment groups but not in the end stage renal failure group) up to 10 fold increases in the exposure of naloxegol were observed.

Despite the higher average exposure in moderately and severely renal function impaired subjects, no clinically meaningful differences were observed in the frequencies or patterns of AEs. In the Phase III pivotal studies, the AE profile of naloxegol in patients with a baseline creatinine clearance value of <60 mL/min was generally similar to that in patients with normal renal function; however, the number of patients in this subgroup was low (n = 45; there were only 36 naloxegol treated patients in this subgroup in the Phase IIb/III pool). No clinically meaningful differences were observed in the frequencies or patterns of AEs.

In subjects with mild or moderate hepatic impairment, the mean naloxegol AUC was 17% and 18% lower than observed in healthy subjects. Cmax was not significantly impacted by mild or moderate hepatic impairment. The safety and tolerability profile of naloxegol in

patients with mild or moderate hepatic impairment at baseline is similar to patients with normal baseline liver function values. There were no clinically relevant changes in laboratory, vital sign, ECG, or physical exam data in the subjects evaluated (Study 10). There is no data in subjects with severe hepatic impairment.

Please also refer to the proposed PI text that is noted in the response.

Evaluator response

This is reasonable. However, after "No clinically meaningful differences were observed in the frequencies or patterns of AEs" should be added "however, numbers were small".

Significant changes in exposure when taken concurrently with P450 inducers or inhibitors or P-gp inhibitors (including food)

Sponsor response

Naloxegol is a sensitive substrate of CYP3A4 and its disposition can be expected to be affected by inhibitors or inducers of this enzyme. Drug-drug interaction studies conducted with a strong, moderate, and weak CYP3A4 inhibitor (ketoconazole, diltiazem, and quinidine, respectively) demonstrated changes in exposure consistent with the class of inhibition (that is, strong: >5 fold increase in AUC, moderate: 2 to 5 fold increase in AUC, and weak: 1.25 to <2 fold increase in AUC. The mean increase in AUC when naloxegol was administered with ketoconazole, diltiazem, or quinidine was approximately 13 fold, 3.4 fold and 1.39 fold, respectively. There is considerable overlap between CYP3A4 and P-gp inhibitors and inducers, and each of the CYP3A4 inhibitors identified above is also classified as an inhibitor of P-gp of which naloxegol is also a substrate.

Rifampin is an inducer of CYP3A4 and P-gp and co-administration with naloxegol resulted in an approximate 1.9 fold decrease in naloxegol AUC compared to naloxegol given alone.

Studies of interactions between naloxegol and morphine, ketoconazole, rifampin, quinidine, and dilitazem have been conducted as part of the naloxegol clinical development program. These findings are presented in detail. The safety profile of naloxegol in these studies was similar to that of the Phase III clinical development program.

AstraZeneca has taken steps to manage the potential for significant changes in exposure to naloxegol caused by CYP3A4/P-gp inhibitors and inducers by:

- contraindicating co-administration of Movantik and strong CYP3A4/P-gp inhibitors
- recommending against co-administration of Movantik with strong CYP3A4/P-gp inducers
- recommending that the starting dose of Movantik be reduced to 12.5 mg when co-administered with a moderate CYP3A4/P-gp inhibitor.

Co-administration of naloxegol with a high fat or a low fat meal resulted in modest increases in mean AUC of approximately 45% and 50%, respectively. The clinical studies have shown that exposure (that is, AUC) increases by 42% to 55% and maximum plasma concentration increases by 30% to 47% when a 25 mg dose of naloxegol is administered after eating a meal, compared with fasting conditions. The DOSAGE AND ADMINISTRATION section of the proposed PI recommends that Movantik is taken once daily in the morning on an empty stomach. AstraZeneca acknowledge that specific dietary constituents (for example, grapefruit juice, star fruit, St. John's wort) can affect CYP3A4 or P-gp and merit specific label language as noted in the PHARMACOKINETICS section of the proposed PI.

The following information is already included in the PRECAUTIONS section of the proposed PI as follows:

CYP3A4 inducers

Movantik should be avoided in patients who are taking strong CYP3A4 inducers (e.g. carbamazepine, rifampicin, St. John's wort) (see INTERACTIONS WITH OTHER MEDICINES).

AstraZeneca proposes the text noted in the response to CER 11.1, in Section 2.7.1 for the DOSAGE AND ADMINISTRATION, Special Populations section of the proposed PI.

Evaluator response

This is noted; however, the evaluator still requests a removal the word 'strong'.

First round assessment of benefit-risk balance

Sponsor response

AstraZeneca believe that the totality of naloxegol data provides evidence for durable and consistent benefits for patients with OIC, which outweigh the observed risks.

Evaluator response

Please see evaluator summary below.

Side effect profile including risk of withdrawal, compared to placebo

Sponsor response

The side effect profile of Movantik is benign and well characterised, and has demonstrated an acceptable safety and tolerability profile both the 25 and 12.5 mg doses. With the exception of GI AEs, discussed further below, AEs with Movantik occurred at low frequencies and were not appreciably different than placebo. The only area of interest where a notable and consistent imbalance versus placebo was identified in the clinical trials was GI AEs. GI adverse drug reactions are not unexpected with naloxegol given its pharmacologic and physiologic effects. The incidence of AEs of abdominal pain and diarrhoea was dose-ordered; most of these events began within the first 7 days of receiving naloxegol and most resolved while the patients were still on study treatment. Clinically important GI AEs (that is, GI SAEs, GI DAEs, and GI events of severe intensity for the preferred terms (PTs) of abdominal pain, abdominal pain upper, abdominal pain lower, diarrhoea, nausea, vomiting, and flatulence) is an identified risk associated with naloxegol. GI perforation, a potential risk associated with naloxegol, was not observed in the development program.

In the Phase III program, analysis of modified Himmelsbach opioid withdrawal scale scores (mHS) demonstrated no treatment imbalance in withdrawal symptoms. A minor imbalance in the number of AEs of opioid withdrawal (naloxegol 25 mg: 5 [1.1%]; naloxegol 12.5 mg: 1 [0.2%]; placebo 1 [0.2%]) was noted to be primarily driven by a small number of patients (n = 4) in the naloxegol 25 mg group with AEs of opioid withdrawal who were receiving methadone as their primary opioid. Theoretically, CNS opioid antagonism could occur in OIC patients with clinical conditions known to disrupt the blood brain barrier (for example, active multiple sclerosis, advanced Alzheimer's disease, uncontrolled epilepsy). However, these patients were specifically excluded from the clinical program and therefore this has not been conclusively demonstrated in clinical trials. As AEs associated with CNS opioid antagonism is a potential risk in patients with potential for blood-brain barrier disruptions, and if prescribed naloxegol, such patients could be at risk for opioid withdrawal and/or impaired analgesia.

Evaluator response

The significant GI side effects were noted in the clinical evaluation report.

The incidence of withdrawal, while noted in the clinical trials as low, may be more prominent when used in a nonclinical trial setting. As such, ensuring it is clear in the PI and RMP are important.

Second round benefit-risk assessment

Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the benefits of Movantik are unchanged from those identified in the first round assessment.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Movantik are unchanged from those identified in the first round assessment.

Second round assessment of benefit-risk balance

The assessment of risk-benefit is unchanged from the first round conclusions.

Second round recommendation regarding authorisation

The evaluator recommends rejecting the submission due to the following major reasons:

- Rationale for the therapy in Australia not given, particularly the difference in the cancer and non cancer populations

This has been justified in the Section 31 response by an assumption that the population is broadly similar to the clinical trial population. Assumptions were made that the cancer population ought to have similar efficacy and safety as the non cancer population, to naloxegol.

Neither assumptions were well justified. However, it is noted that there are several million people in Australia with constipation and taking opioids who would be eligible to take the therapy if registered.

The cancer issue is particularly difficult as there is no data and yet there are a large number of theoretical concerns both about whether there is a need (that is, low recruitment to studies and current availability in Australia of effective therapies in this group), as well as concerns about efficacy and safety in this group.

- Clinical relationship of increase in SBM or 1 or more per week is not clear.

The clinical relevance of this (as opposed to QOL) is still not clear. QOL data provided is not convincing to the evaluator, and in addition was not a primary endpoint.

- Lack of relationship between increase in SBM or 1 or more per week and symptoms.

This was not addressed satisfactorily.

- Side effect profile including risk of withdrawal, compared to placebo, prominent.

This was addressed by agreeing to some changes in the RMP and changes in the PI; however, many of the requested PI changes were not agreed by the sponsor.

Overall, the clinical relevance of the endpoint is unclear. The QoL data was underpowered and not clearly beneficial across all domains. The side effect profile for GI effects is dominant. For this reason, the risk-benefit is positive and the requested indication is not recommended.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU-RMP (version 5, dated 18 September 2014, data lock point 1 June 2013) and an Australian Specific Annex (ASA) (version 1, dated 17 December 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 14.

Table 14: Ongoing safety concerns.

Important identified risks	• Clinically important gastrointestinal adverse events • Opioid withdrawal syndrome • Interactions with drugs modulating CYP3A4 and P-gp activities
Important potential risks	• Gastrointestinal perforation • Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) • Off-label use • Interference with opioid-mediated analgesia
Missing information	• Efficacy/safety in methadone treated population • Efficacy safety in cancer pain population • Efficacy/safety in high risk cardiovascular patients • Efficacy/safety beyond 1 year • Efficacy/safety in patients >75 years of age • Efficacy/safety in patients with severe renal impairment (creatinine clearance <30mL/min) • Efficacy/safety in patients with hepatic impairment • Efficacy/safety in non-Caucasian and non-African-Americans/Black patients • Efficacy/safety in Paediatric populations • Efficacy/safety in Pregnancy/lactation

RMP reviewer comment

'Efficacy/safety in short term opioid treatment' should be added as an item of missing information.

'Efficacy/safety in patients receiving opioids for opioid dependence' should be added as an item of missing information.

Appropriate pharmacovigilance and risk minimisation should be applied to the recommended additional items of missing information.

Otherwise, subject to the evaluation of the nonclinical and clinical aspects of the Safety Specification, the summary of safety concerns is considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance is proposed for a number of safety concerns. Routine pharmacovigilance includes the use of a targeted follow-up questionnaire for adverse event reports relating to the important potential risk 'Gastrointestinal perforation'.

The following additional pharmacovigilance activities are also proposed in the EU RMP (note that no Australian subjects are to be included in these studies) (Table 15).

Table 15: Ongoing safety concerns.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Study D3820C00016 Multiple Dose paediatric pharmacokinetic and safety study.	Missing information: Safety in paediatric populations	An open label, sequential, multiple oral dose study to assess the pharmacokinetics and safety of naloxegol in paediatric patients aged ≥ 6months to < 18 years with opioid-induced constipation following multiple oral dosing. The study will assess single-dose PK as well as multiple dose PK, safety and tolerability for up to 6 months.	Estimated 4Q2016
Study D2288R00081 Post-market observational drug utilisation study	All identified and potential risks and missing information.	To describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol. To describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up.	First annual report delivered end of 4Q2016 and every year thereafter until completion.
Study D2288R00082 Post-market observational safety study in patients taking opioids for cancer pain	All identified and potential risks and missing information.	To estimate event rates for pre-specified Health outcomes of interest among naloxegol treated patients with active cancer pain.	First annual report delivered end of 4Q2016 and every year thereafter until completion.
Study D2288R00084 Post-market observational safety study in patients taking	Identified and potential risks and missing information	To estimate event rates for pre-specified. Health outcomes of	First annual report delivered by the end of 4Q2016 and every year thereafter

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
opioids for non-cancer pain.		interest among naloxegol treated patients with non-cancer pain.	until completion.
Cardiovascular Study A US post-marketing, comparative, observational study to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid-induced constipation.	Cardiovascular risk (missing information: efficacy/safety in high risk cardiovascular patients)	This observational study will characterize the CV risk and major adverse event cardiac events such as myocardial infarction, cerebrovascular accident and cardiac death.	Final report estimated December 2023. Annual reports starting in 2016 until study completion.

RMP reviewer comment

The evaluator has no objection to the pharmacovigilance plan proposed. Although Australian patients will not be included in the proposed studies it is considered that the results will be broadly applicable to the Australian context.

Therefore it is expected that the sponsor will notify the TGA of the results of all pharmacovigilance activities via appropriate mechanisms. This may include reporting in Periodic Safety Update Reports (PSURs) and/or applications to amend the product registration details.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation only is sufficient to mitigate the safety concerns attributed to naloxegol.

No additional risk minimisation activities are proposed.

RMP reviewer comment

Subject to the outcome of the clinical and nonclinical evaluation the proposal to employ routine risk minimisation activities is currently acceptable, as long as recommendations relating the PI/CMI document are adopted in totality.

Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR, and the OPR's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports, respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed

to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

AstraZeneca agrees to provide any relevant and necessary safety information in the RMP required to address safety considerations raised by the nonclinical and clinical evaluators or Evaluation reports.

Evaluator's comment

This is acceptable from an RMP perspective.

Recommendation #2 in RMP evaluation report

It is highlighted to the Delegate that the indication sought in Australia is less restrictive than the indications in the EU and US in that it does not specify "chronic non-cancer pain" and is not proposed as second line after laxatives. It is noted that 'Efficacy/safety in cancer pain population' is an item of missing information in the EU RMP. A large proportion of patients treated with chronic opioid therapy have cancer and unless that population is specifically excluded in the indication it is more likely that there will be considerable use in this group. The proposed Australian indication would also allow for treatment of OIC in patients taking opioids for indications other than for pain.

Sponsor response

It is AstraZeneca's position that Movantik has a favourable benefit/risk profile in OIC patients with cancer pain and that these patients should not be excluded from treatment based on the currently available evidence, especially considering that these patients are more likely to value any improvement in QOL compared with non-cancer pain patients, as noted by the clinical evaluator above.

Evaluator's comment

The sponsor's response is noted.

Whether the evidence supports naloxegol treatment in cancer patients is a matter for the clinical evaluator and the Delegate.

Recommendation #3 in RMP evaluation report

The RMP considers safety information relating to a non-cancer treatment group however the indication proposed for Australia does not specifically exclude cancer patients. Cancer patients are more likely to be generally unwell compared to non-cancer patients. Therefore, it is not unreasonable to consider that AEs are likely to be higher in the cancer population, although this is not known. Given the clinical development program specifically excluded cancer patients, the sponsor should justify how the EU RMP (specifically related to non-cancer) is applicable to the broad indication proposed in Australia, which would include cancer patients.

Sponsor response

There is no published evidence that opioid receptor pharmacology, density, or location in cancer pain patients is substantially different from that of non-cancer pain patients. Therefore, it is AstraZeneca's position that there is no scientific rationale to expect the pharmacodynamic properties of naloxegol to differ between these patient populations. Data from other PAMORAs support no decrease in efficacy in patients with OIC and cancer pain: 2 Phase III studies using methylnaltrexone administered subcutaneously to treat

patients with OIC and advanced illness (59% and 81%, respectively, had cancer pain),[25] and 1 Phase II study using oral prolonged release oxycodone/naloxone to treat OIC patients with moderate/severe cancer pain.[26] Furthermore, in 1 of the studies,[27] a logistic regression analysis of methylnaltrexone treated patients found that rescue free laxation within 4 h of the first dose did not vary according to diagnosis (cancer/non-cancer).

Based on data from trials conducted with other PAMORAs in patients with non-cancer pain, there are no known substantive attributable differences in the safety profile of these drugs for patients with cancer pain.[28]

AstraZeneca has proposed the following text in the proposed PI:

Under PRECAUTIONS:

> ***Cancer-related pain***
>
> *There is very limited clinical experience with the use of Movantik in OIC patients with cancer-related pain. Therefore caution should be used when prescribing Movantik to such patients.*
>
> *Under CONTRAINDICATIONS (new text underlined):*
>
> *Patients with underlying cancer who are at heightened risk of GI perforation, such as those with:*
>
> - *underlying malignancies of gastrointestinal tract or peritoneum*
> - *recurrent or advanced ovarian cancer*
> - *vascular endothelial growth factor (VEGF) inhibitor treatment.*

Evaluator's comment

The sponsor's response is noted.

Whether the evidence supports naloxegol treatment in cancer patients is a matter for the clinical evaluator and the Delegate.

Recommendation #4 in RMP evaluation report

'Efficacy/safety in short term opioid treatment' should be added as an item of missing information.

Sponsor response

AstraZeneca considers that the safety concerns of 'efficacy/safety in short term opioid treatment and in patients receiving opioids for opioid dependence' are encompassed under 'off label use'. Four post authorisation safety study (PASS) studies will be conducted as additional pharmacovigilance activities for Naloxegol. The protocols of these PASS studies are currently under completion. Any results from these PASS studies will be reported when available in the appropriate PBRER and/or RMP.

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[25] Thomas J, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med.* 358: 2332-43 (2008); Slatkin N, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol.* 7: 39-46 (2009).

[26] Ahmedzai SH, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med.* 26: 50-60 (2012).

[27] Thomas J, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med.* 358: 2332-43 (2008).

[28] Thomas J, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med.* 358: 2332-43 (2008); Slatkin N, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol.* 7: 39-46 (2009); Ahmedzai SH, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med.* 26: 50-60 (2012).

Evaluator's comment

The sponsor's response is acceptable in the context of this evaluation.

Recommendation #5 in RMP evaluation report

'Efficacy/safety in patients receiving opioids for opioid dependence' should be added as an item of missing information.

Sponsor response

Movantik is not indicated for use in patients receiving opioids for opioid dependence as it represents off-label use of the product, and off label use is already listed in the RMP as an important Potential Risk. AstraZeneca disagrees with the suggestion and has not included it in the RMP.

Evaluator's comment

The sponsor's response is acceptable in the context of this evaluation.

Recommendation #6 in RMP evaluation report

Appropriate pharmacovigilance and risk minimisation should be applied to the recommended additional items of missing information.

Sponsor response

AstraZeneca agrees to apply appropriate pharmacovigilance and risk minimisation to the recommended additional items of missing information.

Evaluator's comment

The sponsor's response is noted.

Recommendation #7 in RMP evaluation report

The evaluator has no objection to the pharmacovigilance plan proposed. Although Australian patients will not be included in the proposed studies it is considered that the results will be broadly applicable to the Australian context. Therefore, it is expected that the sponsor will notify the TGA of the results of all pharmacovigilance activities via appropriate mechanisms. This may include reporting in PSURs and/or applications to amend the product registration details.

Sponsor response

AstraZeneca agrees to notify the TGA of the results of all pharmacovigilance activities via appropriate mechanisms, including reporting in PSURs and/or applications to amend the product registration details, as available.

Evaluator's comment

The sponsor's response is acceptable in the context of this evaluation.

Recommendation #8 in RMP evaluation report

Given naloxegol is now registered in several countries it is expected that the medication error and off-label use sections of the EU-RMP will be updated with post marketing data as it becomes available.

Sponsor response

AstraZeneca agrees to update all relevant sections of the EU RMP will be updated with post marketing data as it becomes available.

Evaluator's comment

The sponsor's response is acceptable in the context of this evaluation.

Recommendation #9 in RMP evaluation report

The following EU SmPC contraindication which does not appear in the proposed PI is considered clinically relevant and should be included unless the sponsor can provide a compelling justification for its omission:

> *Conditions in patients with cancer pain*
>
> *Patients with underlying cancer who are at heightened risk of GI perforation, such as those with:*
>
> - *underlying malignancies of gastrointestinal tract or peritoneum*
> - *recurrent or advanced ovarian cancer*
> - *vascular endothelial growth factor (VEGF) inhibitor treatment.*

Sponsor response

AstraZeneca acknowledges the evaluator's comment and proposes adoption of this language in the proposed PI.

Under CONTRAINDICATIONS (new text underlined, deleted text in strikethrough):

> ~~***Conditions in patients with cancer pain***~~
>
> *Patients with underlying cancer who are at heightened risk of GI perforation, such as those with:*
>
> - *underlying malignancies of gastrointestinal tract or peritoneum*
> - *recurrent or advanced ovarian cancer*
> - *vascular endothelial growth factor (VEGF) inhibitor treatment.*

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #10 in RMP evaluation report

The CYP3A4 contraindication should also contraindicate the concomitant consumption of grapefruit juice as it does in the EU SmPC.

Sponsor response

AstraZeneca acknowledges the evaluator's comment and proposes to include additional clarification in the proposed PI (new text underlined, deleted text in strikethrough).

> ***CONTRAINDICATIONS***
>
> *Concomitant use with dual P-gp/strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir) or strong CYP3A4 inhibitors (e.g. voriconazole, grapefruit or grapefruit juice ~~when consumed in large quantities~~) can significantly increase exposure to naloxegol and is contraindicated (see INTERACTIONS WITH OTHER MEDICINES).*

The sponsor has advised that there are other PI statements regarding concomitant consumption of grapefruit juice in the *Interactions with Other Medicines* section.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #11 in RMP evaluation report

The 'Clinically important disruptions of the blood-brain barrier' precaution should include the additional examples of CNS metastases and primary brain malignancy, especially in the case that the current indication does not specifically exclude cancer patients.

Sponsor response

AstraZeneca acknowledges the evaluator's comment and proposes to include additional clarification in the PRECAUTIONS section of the proposed PI as follows (new text underlined).

> ***Clinically important disruptions of the blood-brain barrier***
>
> *Movantik is a PAMORA with restricted access to the central nervous system (CNS). Patients with clinically important disruptions to the bloodbrain barrier (eg, primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, recent brain injury, advanced Alzheimer's disease) were not included in clinical studies and may be at risk for naloxegol entry into the CNS. Movantik should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal or reversal of analgesia. If evidence for opioid-mediated interference with analgesia or opioid withdrawal syndrome occurs, patients should be instructed to discontinue Movantik and contact their physician.*

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #12 in RMP evaluation report

The 'Clinically important disruptions of the blood-brain barrier' precaution in the EU SmPC includes the sentence:

> *If evidence for opioid-mediated interference with analgesia or opioid withdrawal syndrome occurs, patients should be instructed to discontinue Moventig and contact their physician.*

This clinically relevant information, relating to the identified risk 'Opioid withdrawal syndrome' and potential risk 'Interference with opioid-mediated analgesia', should be included in the corresponding precaution in the PI.

Sponsor response

AstraZeneca agrees to add the proposed sentence in the question above in the corresponding precaution in the PRECAUTIONS section of the proposed PI (please refer to previous response).

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #13 in RMP evaluation report

The 'Concurrent methadone use' precaution, relating to the missing information 'safety/efficacy in methadone treated population' should match the EU SmPC precaution which contains additional clinically relevant information as follows (additional sentences underlined):

> *Concurrent methadone use*

Patients taking methadone as primary therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse reactions (such as abdominal pain and diarrhoea) than patients not receiving methadone. In a few cases, symptoms suggestive of opioid withdrawal when taking naloxegol 25 mg were observed in patients taking methadone for their pain condition. This was observed in a higher proportion of patients taking methadone than those not taking methadone. Patients taking methadone for treatment of opioid addiction were not included in the clinical development programme and use of naloxegol in these patients should be approached with caution.

Sponsor response

AstraZeneca agrees to add the proposed text as indicated in the question above in the corresponding precaution in the PRECAUTIONS section of the proposed PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #14 in RMP evaluation report

Regarding the recommended item of missing information 'Efficacy/safety in patients receiving opioids for opioid dependence' the PI should include a precaution stating that naloxegol has not been studied in patients being treated for opioid dependence and is not recommended in this group. This is particularly important given some opioid dependence treatments contain naloxone which when combined with naloxegol may increase the risk of precipitating opioid withdrawal.

Sponsor response

AstraZeneca agrees to add the proposed sentence in the question above in the corresponding precaution in the PRECAUTIONS section of the proposed PI (please refer to previous response).

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #15 in RMP evaluation report

Regarding the identified risk 'Gastrointestinal reactions' the following EU SmPC precaution, which does not appear in the proposed PI should be included:

Gastrointestinal adverse reactions

Reports of severe abdominal pain and diarrhoea have been observed in clinical trials with the 25 mg dose, typically occurring shortly after initiation of treatment. There was a higher incidence of discontinuations in patients taking the 25 mg dose compared to placebo due to diarrhoea (0.7% for placebo versus 3.1% for naloxegol 25 mg) and abdominal pain (0.2% versus 2.9%, respectively). Patients should be advised to promptly report severe, persistent or worsening symptoms to their physician. Consideration may be given to lowering the dose to 12.5mg in patients experiencing severe gastrointestinal adverse events depending upon the response and tolerability of individual patients.

Sponsor response

AstraZeneca agrees to add the proposed text as indicated in the question above in the PRECAUTIONS section of the proposed PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #16 in RMP evaluation report

Regarding the identified risk 'Opioid withdrawal syndrome' the following EU SmPC precaution, which does not appear in the proposed PI should be included:

> *Opioid withdrawal syndrome*
>
> *Cases of opioid withdrawal syndrome have been reported in the naloxegol clinical programme (DSM-5). Opioid withdrawal syndrome is a cluster of three or more of the following signs or symptoms: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinnorrhea, pupillary dilation or piloerection or sweating, diarrhoea, yawning, fever or insomnia. Opioid withdrawal syndrome typically develops within minutes to several days following administration of an opioid antagonist. If opioid withdrawal syndrome is suspected the patient should discontinue Moventig and contact their physician.*

Sponsor response

AstraZeneca agrees to add the proposed text as indicated in the question above in the PRECAUTIONS section of the proposed PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #17 in RMP evaluation report

Regarding the item of missing information 'Efficacy/safety in high risk cardiovascular patients' the following EU SmPC precaution, which does not appear in the proposed PI should be included:

> *Patients with CV conditions*
>
> *Naloxegol was not studied in the clinical trial programme in patients who had a recent history of myocardial infarction within 6 months, symptomatic congestive heart failure, overt cardiovascular (CV) disease or patients with a QT interval of ≥500 msec. Moventig should be used with caution in these patients. A QTc study performed with naloxegol in healthy volunteers did not indicate any prolongation of the QT interval.*

Sponsor response

AstraZeneca agrees to add the text proposed by the RMP evaluator in the PRECAUTIONS section of the PI.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Recommendation #18 in RMP evaluation report

Regarding the item of missing information 'Efficacy/safety in patients with severe renal impairment' it is noted that the EU SmPC advises decreasing the starting dose to 12.5 mg in the setting of severe renal impairment whereas the proposed PI does not. This disparity is highlighted for the Delegate's consideration.

Sponsor response

With regard to dose administration, it is AstraZeneca's intention to align the Australian PI with the European SmPC. AstraZeneca agrees to add the proposed text in the DOSAGE AND ADMINISTRATION section of the proposed PI as noted.

Evaluator's comment

The sponsor's response is acceptable from an RMP perspective.

PI amendments are subject to final approval by the Delegate.

Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 Request has adequately addressed the issues identified in the RMP evaluation report.

There is one minor outstanding issue (see below).

Outstanding issues

Issues in relation to the RMP

According to the sponsor's response:

> *AstraZeneca accepts the recommendation and agrees to provide missing information for efficacy/safety in short-term opioid treatment to the Australian Specific Annex (ASA).*

The ASA should be amended accordingly and submitted to the TGA when available.[29]

The clinical evaluator has made recommendations relating to the safety specification which should be considered.

PI amendments made in response to the RMP evaluation report are subject to final approval by the Delegate.

Comments on the safety specification of the RMP

Clinical evaluation report

- The Safety Specification in the draft RMP is satisfactory. Vigilance on Drug Induced Liver Injury (DILI) and arthralgia is specifically required.

Based on this recommendation, the Delegate may wish to direct the sponsor to include 'Drug Induced Liver Injury' and 'Arthralgia' as a specific safety concern in the RMP.

Nonclinical evaluation report

- Results and conclusions drawn from the nonclinical program for Movantik detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

[29] Sponsor comment: "This issue was later resolved."

Implement EU RMP (version 5, dated 18 September 2014, DLP 1 June 2013) and an ASA (version 1, dated 17 December 2014) to be revised to the satisfaction of the TGA (see section 1) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections in respect of Biopharmaceutics to registration of these products. A matter relating to the quality control of the finished products that is stated in the Quality Summary to be unresolved was resolved on 13 October 2015.

Both strength tablets are oval, biconvex, mauve, film coated tablets debossed with "nGL" on one side. The 12.5 mg and 25 mg tablets are debossed with "12.5" and "25" respectively on the other side. The tablets will be marketed in OPA/aluminium/PVC//aluminium blisters.

The drug substance is manufactured by a complex, convergent synthesis. Two non-solvated polymorphic forms were described (Forms A and B) and Form B is the only form that can be obtained under proposed commercial manufacturing conditions.

The drug substance is Biopharmaceutics Classification System (BCS) Class 3; while highly soluble (> 50 mg/mL) across the physiological pH range, permeability data assessed across Caco-2 cell monolayers indicate the drug substance has low permeability. Naloxegol oxalate exhibits 2 pKa values: 8.4 (amine) and 9.5 (phenol), and that LogP = 1.4 in octanol/water. No limits are applied to the particle size distribution of the drug substance due to its high aqueous solubility, and because variability in the particle size distribution also had no impact on tablet hardness, content uniformity or overall finished product stability.

Three relative bioavailability and bioequivalence clinical studies were conducted to create a link between the various naloxegol formulations that have been used during clinical development. Bioequivalence between the formulations was demonstrated. Food resulted in a substantial increase in AUC and naloxegol is recommended to be taken on an empty stomach.

Nonclinical

There are no nonclinical objections to the registration. Naloxegol is a μ-opioid receptor antagonist in vitro that did not affect opiate analgesia in a rat model except at high doses. In rats, oral naloxegol reversed morphine induced small intestinal ileus. The PEGylation of naloxone to produce naloxegol does not affect μ-opioid receptor antagonism and, desirably, reduces κ and δ opioid receptor affinity. Naloxegol has a low risk of producing adverse cardiovascular effects.

The nonclinical evaluator considered that naloxegol is unlikely to affect gastric emptying or to induce ileus at human clinical exposures. Naloxegol did not trigger opiate-induced physical withdrawal, physical dependence, drug seeking and/or addictive behaviours, analgesia, or overt psychoactive effects in rats. Supratherapeutic doses of naloxegol modified addictive behaviours in rats (partial to complete reversal of the discriminative effects of morphine; NOAEL ≈ the proposed clinical dose).

The oral bioavailability of naloxegol is low and dose dependent. This is likely due to saturation of enterothelial ABC B1, a potential source of drug-drug interactions. Fasting doubles oral bioavailability. In rats this effect varied with sex, females having a lower Tmax and higher Cmax and an AUC approximately double that of males. That difference was consistent with sex differences in enterothelial ABC B1 efflux transporters and is species specific. Naloxone-PEG≥ 5 conjugates have negligible blood brain barrier (BBB) penetrance.

Naloxegol is mostly excreted within 48-72 h, and faeco-biliary elimination predominates. Under therapeutic conditions naloxegol is not a CYP inhibitor or inducer. Naloxegol is an ABC B1 efflux transporter substrate but does not inhibit this transporter or OATP1B1, OATP1B3 or BCRP. Inhibition of enterothelial OATP1A2 efflux transporters is a well known cause of drug interactions, but effects on OATP1A2 were not evaluated. Although naloxone inhibits enterothelial OATP1A2, the sponsor claims that an effect of naloxone on OATP1A2 substrates in vivo has not been reported in clinical studies, and that potential naloxegol-OATP1A2 interactions are unlikely.

Naloxegol is not genotoxic per se but several of its impurities/degradants are, although these have been adequately qualified at the proposed specifications. Naloxegol is not a human-relevant carcinogen. A naloxegol-mediated effect on vertebral arch development in rabbits at high relative exposures (non-maternotoxic to minimally maternotoxic exposures) cannot be categorically excluded, supporting a pregnancy category of B3. Naloxegol may concentrate in milk in lactating rats, and treatment at a high dose through gestation and lactation delayed male F1 development. Because of its affinity for ocular melanin, naloxegol (or its metabolites) may produce retinal effects such as dyschromatopsias, though there was no evidence of ocular toxicity in animal studies.

Clinical

Pharmacology

Naloxegol undergoes rapid absorption from the gut with peak plasma concentrations attained around 2 h (0.5-3 h) after ingestion of a single dose. A secondary plasma concentration peak due to enterohepatic recycling is likely to occur. At therapeutic doses, mean terminal elimination half-life values across the clinical pharmacology studies ranged from 6 to 11 h. Naloxegol exposure is dose-proportional at therapeutic doses and up to 100 mg. Following multiple dosing, steady state is achieved within 2 to 3 days. Absolute bioavailability has not been assessed.

The formulation of the tablets proposed for registration differs from the formulation used in the pivotal clinical trials but the 25 mg commercial tablet has been demonstrated to be bioequivalent to the clinical trial formulation. A biowaiver was accepted for the 12.5 mg based on the similarity in composition, in vitro dissolution profile, manufacturing method, and the linear PK observed over the relevant dose range. The effect of food was examined on the proposed commercial formulation. A high fat meal increases bioavailability of naloxegol with AUC increased by ~45% and Cmax by ~30%. The sponsor has recommended naloxegol be taken at least 30 minutes prior to the first meal of the day or 2 hours post-meal.

The primary route of naloxegol elimination is hepatic metabolism. Non-renal clearance is predominantly via faecal excretion (direct and biliary secretion). Six metabolites were identified none of which have been identified as unique or disproportionate human metabolites. The major plasma circulating species is naloxegol.

CYP3A is the major CYP enzyme responsible for the metabolism of naloxegol. Naloxegol is also a substrate of the P-gp transporter. Interaction studies demonstrated clinically

significant interactions with ketoconazole, a dual strong CYP3A4 and P-gp inhibitor with a ~13 fold increase in AUC for naloxegol on concomitant administration. Diltiazem, a dual moderate CYP3A4 and P-gp inhibitor resulted in ~3 fold increase in AUC and quinidine, a dual weak CYP3A4 and P-gp inhibitor resulted in a~1.4 fold increase in AUC. A population PK analysis showed generally similar results, that is, an 8.1 fold higher naloxegol exposure (for AUC and Cmax) with strong CYP3A4 inhibitors, increase in AUC and Cmax by about 60% and 30% with moderate CYP3A4 inhibitors, and little change in naloxegol exposure with weak inhibitors.

A single dose study was conducted in patients with renal impairment which showed somewhat increased exposure in subjects with moderate and severe renal impairment but no significant change in subjects with end stage renal disease on dialysis. A single dose study compared the pharmacokinetics in healthy subjects and subjects with mild and moderate hepatic disease (Child-Pugh Class A and B). Results of that study suggest no difference in drug levels. However, this was a small, single dose study, with only 8 subjects in each group.

A population PK analysis of the Phase III studies indicated that patients with OIC had ~30% higher exposure to naloxegol than participants in Phase I studies or the Phase IIb study, many of whom were healthy. The sponsor suggests that error and uncertainty in dosing and/or sampling times (that is, rich sampling in Phase IIb study versus sparse sampling in the Phase III studies), different food consumption patterns, and other underlying medical conditions in the Phase III patient populations may have contributed to these differences.

Subjects below 18 years of age have not received naloxegol in clinical trials. A total of 142 subjects aged ≥65 years and 24 aged ≥75 years received naloxegol in Phase III studies. The mean age of patients in these studies was 52 years. A small increase in naloxegol exposure was seen with increasing age.

Only one PD study was included in the submission. This was to assess potential signals of QT prolongation. The QT study confirmed in vitro data findings and showed that naloxegol did not prolong QTcF beyond 10 msec.

Efficacy

Study 003 was a Phase II dose finding study. Study subjects were to take from 5 mg through to 100 mg naloxegol daily over 4 weeks but the 100 mg dose was not pursued after safety issues were identified with the 50 mg dose. A total of 207 subjects were randomised and received at least one dose of study medication. Randomisation was stratified by total daily opioid dose at screening in morphine equivalent units (MEU) with the low morphine equivalent (MEQ) group taking from 30 to 100 MEU daily and the high MEQ group taking > 100 to 1000 MEU daily. During double blind treatment, naloxegol treated patients had more SBMs than placebo treated patients at all post dose timepoints. The mean number of SBMs/week across the 28 day double blind period increased with each successive dosing cohort, from 4.2 SBMs/week for 5 mg patients to 4.6 SBMs/week for 25 mg patients to 6.2 SBMs/week for 50 mg patients. The mean change in SBMs/week from baseline across the 28 day double blind period by cohort and opioid dose (high or low) is shown below in Table 16.

Table 16: Mean change in SBMs/week from baseline across the 28-day double-blind period by cohort and opioid dose (high or low).

Naloxegol dose	Low MEQ		High MEQ	
	Placebo	Active	Placebo	Active
5 mg	3	1.8	1	2.7
25 mg	2.1	4.1*	1.3	2.7*
50mg	1.5	4.5*	0.9	4.6*

P ≤ 0.05

The above study showed that for subjects with OIC taking either low or high doses of opioids there appears to be a dose response between the naloxegol 25 mg and 50 mg daily doses and the 5 mg daily dose was not effective in reducing OIC.

Doses of 12.5 mg, and 25 mg daily naloxegol were compared with placebo in Studies 04 and 05, the pivotal studies. These studies were randomised, double blind, placebo controlled studies to assess the efficacy and safety of NKTR-118 (naloxegol) in patients with non-cancer related pain and OIC. The primary objective was to compare the efficacy of naloxegol 12.5 mg and 25 mg with placebo in the treatment of patients who have OIC. The study duration was up to 18 weeks, consisting of an initial screening period of up to 2 weeks, a 2 week OIC confirmation period during which the diagnosis of OIC and stability of the opioid regimen were confirmed, a 12 week treatment period, and a follow-up visit 2 weeks after the last dose of study drug.

Patients were required to have OIC defined as <3 spontaneous bowel movements per week and to report ≥1 of the following symptoms in at least 25% of the bowel movements (BM) recorded in the electronic diary during the 2 week the OIC confirmation period: BSS stool type 1 or 2; moderate, severe, or very severe straining; incomplete BM. A minimum of 50% of patients were to meet criteria for being laxative inadequate responders (LIR) prior to commencing naloxegol. LIR patients with OIC were defined as those who take laxatives at least four times over a 2 week period and reported at least moderate or greater severity on at least one item of the Stool Symptom Screener. The non LIRs, represented patients who take laxatives with less frequency or not at all and report a range of severity on the Stool Symptom Screener items. Major exclusion criteria were: constipation due to other causes; cancer pain; CrCL <60 mL/min; recent myocardial infarction (MI), symptomatic congestive heart failure, or any other overt cardiovascular disease; potential BBB disruptions; requirement for strong CYP3A4 inhibitors, opioid antagonists, mixed opioid agonists/ antagonists or laxatives. Patients were required to stop all laxatives and other bowel regimens including prune juice and herbal products throughout the 2 week OIC confirmation period and the 12 week treatment period.

After screening, patients received 12.5 mg or 25 mg of naloxegol or placebo once daily an hour before eating in the morning for 12 weeks. Bisacodyl 5 mg was used as rescue medication. The primary efficacy outcome was response to study drug during Weeks 1 to 4, where a responder is defined as having at least 3 SBM/week, with at least 1 SBM/week increase over baseline, for at least 3 out of the first 4 weeks. Efficacy assessments to Week 12 were secondary. SBM was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 h.

A total of 1750 patients were enrolled in Study 04 with 652 randomised. 1969 patients were enrolled in Study 05 with 700 randomised. In the combined studies, most patients were white (79%), 62.4% were female and mean age was 52.2 years with 148 patients (11%) aged ≥65 years. The mean daily morphine equivalent dose ranged from 135.6

µ/day to 143.2 µ/day in Study 04 and from 119.9 µ/day to 151.7 µ/day in Study 05. At baseline, approximately 79% of patients were receiving <200 µ/day total daily dose of opioids and approximately 67% of patients were taking strong opioids as their maintenance treatment for pain. The median numerical rating scale pain score at baseline in the pooled data for Studies 04 and 05 was 4.8 on an 11 point scale, suggesting that patients' pain level remained moderate despite ongoing opioid treatment. The 3 most frequent complaints with constipation were infrequent defecation, straining, and hard stools. At baseline (OIC confirmation period), the mean number of SBMs per week was low (range 1.3 to 1.6) across treatment groups.

The mean duration of exposure to study treatment of approximately 75 days was similar across the treatment groups in both studies. A total of 887 patients with OIC were exposed to naloxegol in the pivotal studies. The higher discontinuation rate in the naloxegol 25 mg groups (10.3%) compared with the naloxegol 12.5 mg (4.8%) groups and placebo groups (5.4%) in both studies was driven primarily by withdrawal due to AEs and patient decision. The response rates in Study 04 were 29.4%, 40.8% and 44.4% for placebo, naloxegol 12.5 mg and naloxegol 25 mg, respectively. Both doses of naloxegol were superior to placebo for response rate from baseline to Week 12. In Study 05 the response rates to Week 12 were 29.3%, 34.9% and 39.7% for placebo, naloxegol 12.5 mg and naloxegol 25 mg, respectively. Only the 25 mg naloxegol dose was superior to placebo for response rate from baseline to Week 12 in that study.

For the majority of endpoints, including response rate the LIR group appear to have a stronger response to naloxegol than the non-LIR group. There is a small dose related increase in SBM/week. Onset of effect was quite rapid with median time to first SBM around 20 hours for patients given 12.5 mg naloxegol and 5-7 h for the 25 mg dose compared with >24 h for patients given placebo.

Use of rescue bisacodyl was low in both studies. Over the 12 week treatment period in Study 04, the median number of times patients used bisacodyl as rescue laxative was 1 for the 25 mg group, 2 for the 12.5 mg group and 4 for the placebo group. In Study 05, the median number of times that patients used bisacodyl as a rescue laxative was 1.0 for the naloxegol 25 mg group, 1.0 for the naloxegol 12.5 group, and 3.0 for placebo. The proportion of patients who used bisacodyl at least once was lower in the naloxegol 25 mg (133 patients; 57.3%) and 12.5 mg (133 patients; 57.3%) groups compared with the placebo group (164 patients; 70.7%).

In Study 04 there was an increase in mean SBMs per week in the naloxegol 25 mg and 12.5 mg groups compared with placebo (0.99; $p < 0.001$, and 0.54; $p = 0.011$, respectively). These numbers correspond to approximately 4.4 SBMs per week in the naloxegol 25 mg group compared with 3.9 and 3.4 SBMs per week in the naloxegol 12.5 mg and placebo groups, respectively. In Study 05, there was an increase in mean SBMs per week in the naloxegol 25 mg and 12.5 mg groups compared with placebo (1.04; $p<0.001$ and 0.52; $p = 0.028$, respectively), and this increase was maintained over the entire 12 week treatment period. These numbers correspond to approximately 4.6 SBMs per week in the naloxegol 25 mg group compared with 4.1 and 3.6 SBMs per week in the naloxegol 12.5 mg and placebo groups, respectively.

A planned study in patients with cancer-related pain was discontinued with only 14 patients enrolled. The sponsor has stated this was due to slow recruitment.

Safety

Safety data were available from the pharmacology and efficacy studies and from Study 07, a 12 week, double blind safety extension study of Study 04 and Study 08, a 12 month safety study. In the Phase IIb and III naloxegol clinical studies, 1497 patients were received naloxegol at 1 or more doses (33 to 5 mg, 446 to 12.5 mg, 999 to 25 mg, and 35 to

50 mg) and were included in the safety analyses. For the 25 mg dose, 464 patients were exposed for at least 24 weeks, 317 were exposed for at least 51 weeks, and 96 were exposed for at least 52 weeks. In the Phase 1 studies, 438 subjects received naloxegol at doses of 5 to 1000 mg.

The most frequently reported AEs in the pivotal trials were abdominal pain, diarrhoea, nausea and vomiting. The overall incidence of these events was low (all <4% in any treatment group). These events increased with the dose of naloxegol, though the overall incidence remained low.

In the pivotal trials AEs of particular interest, including selected CV events (that is, major adverse cardiac events, congestive heart failure), AEs potentially related to blood pressure changes, serious GI events adjudicated for bowel perforation, AEs potentially related to abuse liability, and AEs potentially related to opioid withdrawal were assessed by central adjudication. Of these events, there was some indication that opioid withdrawal effects were more frequent in patients given naloxegol and that these events were more frequent with the 25 mg dose than with the 12.5 mg dose.

A consultant report produced for the FDA described the sponsor's analysis and FDA post hoc analyses for AEs consistent with withdrawal effects and found that the incidence was low in all analysis. The analysis using the MedDRA Standardised MedDRA Queries (SMQ) for possible drug withdrawal syndrome showed that 1.1% of patients given 25 mg naloxegol in the pivotal studies had an AE consistent with drug withdrawal symptoms compared with 0.5% of patients given 12.5 mg naloxegol and 0.2% of patients given placebo.

There was no signal for cardiovascular adverse effects or gut perforation in those studies.

Risk management plan

There were no pharmacovigilance concerns that would preclude approval. The sponsor has proposed routine pharmacovigilance and a drug utilisation study. The RMP evaluator has noted a high risk of off-label use. The clinical evaluator has recommended that the Safety Specification in the draft RMP specifically include DILI and arthralgia.

The recommended condition of registration for the RMP is that the sponsor implement EU RMP (version 5, dated 18 September 2014, DLP 1 June 2013) and an ASA (version 1, dated 17 December 2014) to be revised to the satisfaction of the TGA and any future updates as a condition of registration.

Risk-benefit analysis

Delegate's considerations

The PK of naloxegol is likely to be quite variable given it is a substrate of CYP3A4 and of P-gp. Strong CYP inhibitors were prohibited in the Phase III clinical trial program and, given the large increase in exposure associated with concomitant ketoconazole, strong CYP3A4 inhibitors and strong P-gp inhibitors should not be given with naloxegol. There are no data on use of naloxegol in children and insufficient data on its pharmacokinetics and safety in patients with cancer, who are likely to have slow gut transit times as well as low body weights and hepatic and/or renal impairment. The PK of naloxegol has not been adequately assessed in subjects with reduced renal function, the primary method of drug elimination and it should not be administered to patients with severe hepatic impairment. Naloxegol has been adequately examined in the elderly population and the PK does not vary to a clinically significant extent with age.

The sponsor has proposed that the dose of naloxegol should be decreased to 12.5 mg daily when co-administered with dual P-gp/moderate CYP3A4 inhibitors (for example, diltiazem, verapamil, erythromycin) however no study assessed that dose combination. The proposal appears to have been based on the results of the interaction study with diltiazem where healthy subjects were given a single 25 mg naloxegol dose and the PopPK analysis of Phase III study data which showed a 60% to 30% increase in AUC for naloxegol given with moderate CYP3A4 inhibitors. Given the safety profile of naloxegol, this appears acceptable.

The pivotal studies were performed in a group of patients taking median doses of opioids that are above the maximum dose recommended for the management of pain in Therapeutic Guidelines - Analgesic, which is 100 mg oral morphine equivalent per day. Despite these high levels of opioids median pain scores were consistent with ongoing moderate pain. The side effect of constipation with opioids is well known and is dose dependent. This group had marked constipation at baseline. The design of the studies was acceptable. These were designed prior to the current guideline under consideration for adoption by the TGA. The major departures from the recommendations in the new guideline were in the assessment of laxative resistance or inadequate response to laxatives, the lack of assessment of rebound and the lack of an active control study.

The selection of primary endpoint, responder analyses and duration of study were consistent with the new guideline. A statistically significant increase in the mean number of SBMs in the target population was demonstrated for the 25 mg daily dose of naloxegol. While OIC signs and symptoms improved in both the placebo and active treatment groups, an additional 10 to 15% of patients given 25 mg naloxegol experienced clinical response compared with placebo. Additionally, patients given naloxegol had a mean of 1 additional SBM/week compared with placebo, though this was a secondary endpoint. From a baseline mean of 1.3 to 1.6 SBM/week, this effect is clinically significant. However, as noted by the clinical evaluator, there were no statistically significant improvements in QOL indicators, though the studies were not designed to specifically assess statistical differences in QOL.

Onset of effect for most patients given the 25 mg dose was within 24 h of commencing treatment. The pivotal clinical studies enrolled patients with OIC who were both responsive and unresponsive to previous laxative therapy and naloxegol was similarly effective in these populations. The effect of a combination of laxatives with naloxegol has not been examined. At this time, consideration should be given to limiting naloxegol to patients who have not responded to simple laxatives due to the limited long term safety data available and the widespread availability of laxatives as established treatments for OIC. There has not been adequate assessment of naloxegol in patients taking opioids for cancer related pain and naloxegol should not be used in this patient group. These patients are more likely to be taking medications that affect the pharmacokinetics of naloxegol, are more likely to have hepatic or renal impairment and more likely to be at increased risk of gut obstruction that other patients.

This product appears to have been developed as an alternative to laxatives rather than as adjunctive treatment because laxatives were not permitted in the clinical trials except for bisacodyl as rescue medication. There were no comparisons of efficacy with current laxative medications. The other major omission is the exclusion of efficacy and safety assessments in patients taking opioids due to pain associated with cancer.

As a laxative alternative this product appears to be adequate and its use as an alternative to laxatives could be reflected in the PI. Ideally, further assessment of the efficacy of naloxegol when used as an adjunct to laxatives in patients with an insufficient or partial response to laxatives will be performed.

Proposed action

The Delegate has no reason to say, at this time, that the application for naloxegol should not be approved for registration subject to negotiation of an indication that reflects the clinical trial evidence of safety and efficacy.

- It is not clear whether naloxegol should be restricted to patients who have an inadequate response to laxatives. The clinical trial included both laxative responsive and patients who had an inadequate response to laxatives. Efficacy and safety were similar in these groups. However, given the long history of use of various laxatives and the lack of comparative efficacy data between naloxegol and any laxative, it may be appropriate to restrict the indications of naloxegol to patients with an inadequate response to laxatives, as has occurred in the EU.
- The extent of benefit is fairly modest with up to 15% of patients receiving a clinically significant response over what occurred with placebo.
- Naloxegol does not appear to have major safety issues. Ensuring the patient does not have a gut obstruction is necessary prior to commencing treatment.
- While opioid withdrawal symptoms may occur these were not common and would be manageable.
- Naloxegol may provide a less invasive solution than enemas for constipation in patients with an inadequate response to available laxatives.
- Naloxegol may be an alternative to laxatives in patients with OIC.

Given the differing causes of constipation in patients with cancer and the increased likelihood of drug interactions and/or hepatic or renal impairment in those patients naloxegol should not be used in that population. Alternative treatments are available.

Request for ACPM advice

The Advisory Committee on Prescription Medicines (ACPM) is requested to provide advice on the following specific issues:

- Does the committee consider that the indications should be restricted to patients with OIC and non-cancer pain?
- Does the committee consider use of naloxegol should be restricted to patients who have had an inadequate response to laxatives? If so, should this be reflected in the indications?
- There are no data on the use of naloxegol with laxatives. Does the committee consider that use of naloxegol with laxatives should be restricted? If so what restrictions would be appropriate?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

AstraZeneca welcomes the opportunity to provide comment on the evaluation associated with the sponsor's application proposing to register the new chemical entity Movantik (naloxegol) for the treatment of OIC. AstraZeneca's comments on the issues for which the advice of the ACPM is sought, as outlined in the Delegate's request for ACPM advice dated 30 October 2015, are presented below.

Sponsor responses

- *Question 1: Does the committee consider that the indications should be restricted to patients with OIC and non-cancer pain?*

AstraZeneca acknowledges the Delegate's concern that there is limited clinical experience of the use of Movantik in OIC patients with cancer related pain and, because of this, agrees caution should be exercised when prescribing Movantik to such patients. A statement has been proposed for the Precautions section of the PI highlighting this aspect.

A review of the literature suggests there is no published evidence that opioid receptor pharmacology, density, or location in cancer pain patients are substantially different from those of non-cancer pain patients. Therefore, there is no scientific rationale to expect the PD behaviour or efficacy of Movantik to differ between these patient populations.

Furthermore, data from trials conducted with other peripherally acting μ-opioid receptor antagonists in patients with non-cancer pain demonstrated that there are no known substantive attributable differences in the safety profile of these drugs for patients with cancer pain compared with patients with non-cancer pain.[30]

The PK of naloxegol were minimally affected in patients with hepatic impairment and mild renal impairment. For OIC patients with cancer pain who are experiencing moderate to severe renal impairment, it is recommended that the prescriber initiate therapy at the lower dose (12.5 mg) until clinical response can be assessed.

Patients with cancer pain suffer from the symptoms associated with their underlying disease, along with the discomfort commonly associated with the therapies used to treat malignancies. Comorbidity with OIC adds to this burden with additional symptoms in patients who typically have a poor prognosis. Because of this, there is a high medical need in this population for tolerable therapies that can alleviate suffering.

AstraZeneca acknowledges the Delegate's comment that OIC patients with cancer pain are at an increased risk of gastrointestinal obstruction, which is why Movantik is contraindicated in patients with underlying cancer who are at heightened risk of gastrointestinal perforation, such as those with underlying malignancies of the gastrointestinal tract or peritoneum, with recurrent or advanced ovarian cancer, or undergoing vascular endothelial growth factor inhibitor treatment.

It is AstraZeneca's position that the decision on whether to prescribe Movantik for OIC patients with cancer pain should be made by the treating physician based on a thorough evaluation of the patient's health status and any concomitant medications. Text is proposed for the PI which gives clarity over the extent of clinical data in different patient populations and offers appropriate precautionary statements regarding use in cancer patients. AstraZeneca believes that restricting the indication in the manner suggested by the Delegate is not necessary and will deny a patient population with high medical need of the option to gain potential benefit from this new oral treatment. This position is aligned with that adopted by the CHMP in the EU, which does not restrict Movantik treatment to patients with non-cancer pain (refer to the Movantik SmPC).

Additional safety data will be collected on an ongoing basis with routine pharmacovigilance activities, as well as a PASS as described in the RMP that will be used to monitor OIC patients with cancer pain (refer to Study D3820R00007). The purpose of this PASS is to estimate individual event rates for outcomes of interest among Movantik

[30] Thomas J, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med.* 358: 2332-43 (2008); Slatkin N, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. *J Support Oncol.* 7: 39-46 (2009); Ahmedzai SH, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med.* 26: 50-60 (2012).

treated patients with active cancer pain. This will provide important missing safety information for the cancer pain population. The first annual report will be delivered by the end of 2016 and every year thereafter until completion, and can be provided to the TGA upon request.

- *Question 2: Does the committee consider use of naloxegol should be restricted to patients who have had an inadequate response to laxatives? If so, should this be reflected in the indications?*

AstraZeneca believes that the use of Movantik should not be restricted to patients who have had an inadequate response to laxatives. As the Delegate has noted, efficacy and safety were similar in both the laxative responder and non-responder subgroups in the Phase III clinical trials. In addition, there are no generally accepted definitions of standard of care for OIC or of inadequate response to laxatives. Moreover, unlike conventional laxatives, Movantik has a specific mechanism that targets the pharmacological cause of OIC, which may be of benefit to patients in both groups, as demonstrated in the clinical trials. For these reasons, AstraZeneca considers that the proposed indication, which does not limit treatment to patients with inadequate response to laxatives, is most appropriate.

- *Question 3: There are no data on the use of naloxegol with laxatives. Does the committee consider that use of naloxegol with laxatives should be restricted? If so what restrictions would be appropriate?*

As stated in the Dosage and Administration section of the proposed PI, laxatives should be discontinued when initiating Movantik therapy. AstraZeneca believes that additional restriction beyond the above dosing recommendation is unwarranted, as supplemental laxative use should be guided by the clinical judgement of the prescriber based on patient response. It should be noted that bisacodyl was allowed in the clinical studies as a rescue therapy. As described in the Summary of Clinical Efficacy, over the 12 week study period, the proportion of patients who used bisacodyl at least once in the placebo, naloxegol 12.5 mg, and 25 mg groups was 72.0%, 63.4%, and 54.7%, respectively, in Study D3820C00004, and 70.7%, 57.3%, and 57.3%, respectively, in Study D3820C00005. Noting that the percentage of patients using rescue bisacodyl at least once and the weekly bisacodyl dose taken were lower in the naloxegol groups compared with the placebo group, this nevertheless provides some clinical experience with concomitant laxative use with naloxegol.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Movantik film coated tablets containing 12.5 mg and 25 mg of naloxegol oxalate to have an overall positive benefit-risk profile for the amended indication;

> *Movantik is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).*

In making this recommendation the ACPM

- Was of the view that the indication should state 'who have had an inadequate response to laxative(s),' similar to the Canadian indication.
- Advised that the indication should not specify use in non-cancer patients only, as there was insufficient reason to exclude use in cancer patients.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- Highlight in the PI that there is no evidence regarding use in combination with laxatives.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- Does the committee consider that the indications should be restricted to patients with OIC and non-cancer pain?

Despite there being no data available in cancer patients, the ACPM advised that there was nothing to indicate that constipation in cancer patients was any different to constipation in non-cancer patients. In addition, the ACPM noted that methylnaltrexone was not restricted to non-cancer patients. There was concern that naloxegol might be used in cancer patients with bowel obstruction. However, the ACPM advised that the PI contained sufficient warning about use in this situation under CONTRAINDICATIONS and that treatment with naloxegol in patients with cancer should be at the discretion of the treating physician.

- Does the committee consider use of naloxegol should be restricted to patients who have had an inadequate response to laxatives? If so, should this be reflected in the indications?

The ACPM advised that it should be restricted to patients who have had an inadequate response to laxatives and that this should be reflected in the indication, similar to the indication recommended in Canada.

- There are no data on the use of naloxegol with laxatives. Does the committee consider that use of naloxegol with laxatives should be restricted? If so what restrictions would be appropriate?

The ACPM noted that the effect of combination laxative use with naloxegol had not been examined. Therefore, use should be limited to patients who have not responded to simple laxatives due to the limited long term safety data available. The ACPM advised that it was unnecessary to restrict use of naloxegol with laxatives due to the widespread availability of laxatives as established treatments for OIC. However, the PI should highlight that there is no evidence regarding use in combination with laxatives.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of

- *Movantik (naloxegol oxalate) 12.5 mg film coated tablet blister pack*
- *Movantik (naloxegol oxalate) 25 mg film coated tablet blister pack*

indicated for:

> *Movantik is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s).*

Specific conditions of registration applying to these goods

- The naloxegol oxalate EU RMP, (version 5, dated 18 September 2014, DLP 1 June 2013) and an ASA (version 1, dated 17 December 2014), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Movantik at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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