PROPHARMACE MOCK REGISTRATION ASSESSMENT 2020
Part 1
RESOURCE PACK

Instructions to candidates

1. This resource pack is available to use for questions 1,4,9,17,27,31,35 and 40.
2. A table of contents is shown on page 2 of this pack.
3. No other reference sources can be brought in to this part of the assessment.

Your answer sheet must be handed in at the end of the assessment.

Print your name and pre-registration number here and sign to confirm that you have read and understood these instructions:

Name……..

Pre-registration trainee number……..

Signature……..

Contents

For use with question 1, *please turn over*:

Dymista 137 micrograms / 50 micrograms per actuation Nasal Spray

Summary of Product Characteristics Updated 10-Dec-2019 | Mylan

1. Name of the medicinal product

Dymista Nasal Spray

137 micrograms / 50 micrograms per actuation

Nasal Spray, Suspension

2. Qualitative and quantitative composition

Each g of suspension contains 1000 micrograms azelastine hydrochloride and 365 micrograms fluticasone propionate.

One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride (= 125 micrograms azelastine) and 50 micrograms fluticasone propionate.

Excipient with known effect:

One actuation (0.14 g) delivers 0.014 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Nasal spray, suspension.

White, homogeneous suspension.

4. Clinical particulars

4.1 Therapeutic indications

Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient.

4.2 Posology and method of administration

Posology

For full therapeutic benefit regular usage is essential.

Contact with the eyes should be avoided.

Adults and adolescents (12 years and older)

One actuation in each nostril twice daily (morning and evening).

Children below 12 years

Dymista Nasal Spray is not recommended for use in children below 12 years of age as safety and efficacy has not been established in this age group.

Elderly

No dose adjustment is required in this population.

Renal and hepatic impairment

There are no data in patients with renal and hepatic impairment.

Duration of treatment

Dymista Nasal Spray is suitable for long-term use.

The duration of treatment should correspond to the period of allergenic exposure.

Method of administration

Dymista Nasal Spray is for nasal use only.

Instruction for use

Preparing the spray:

The bottle should be shaken gently before use for about 5 seconds by tilting it upwards and downwards and the protective cap be removed afterwards. Prior to first use Dymista Nasal Spray must be primed by pressing down and releasing the pump 6 times. If Dymista Nasal Spray has not been used for more than 7 days it must be reprimed once by pressing down and releasing the pump.

Using the spray:

After blowing the nose the suspension is to be sprayed once into each nostril keeping the head tilted downward (see figure). After use the spray tip is to be wiped and the protective cap to be replaced.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (see section 4.5).

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Dymista Nasal Spray undergoes extensive first-pass metabolism, therefore the systemic exposure of intranasal fluticasone propionate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events.

Caution is advised when treating these patients.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

In general the dose of intranasal fluticasone formulations should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. Higher doses than the recommended one (see section 4.2) have not been tested for Dymista. As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently.

Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses. Since growing up is also given in adolescents it is recommended that the growth of adolescents receiving prolonged treatment with nasal corticosteroids is regularly monitored, too. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Close monitoring is warranted in patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts.

If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to Dymista Nasal Spray.

In patients who have tuberculosis, any type of untreated infection, or have had a recent surgical operation or injury to the nose or mouth, the possible benefits of the treatment with Dymista Nasal Spray should be weighed against possible risk.

Infections of the nasal airways should be treated with antibacterial or antimycotical therapy, but do not constitute a specific contraindication to treatment with Dymista Nasal Spray.

Dymista contains benzalkonium chloride. It may cause irritation of the nasal mucosa and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Fluticasone propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after intranasal dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects. Co-treatment with other CYP 3A4 inhibitors, including cobicistat-containing products is also expected to increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side effects.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole), as there is potential for increased systemic exposure to fluticasone propionate.

Azelastine hydrochloride

No specific interaction studies with azelastine hydrochloride nasal spray have been performed. Interaction studies at high oral doses have been performed. However, they bear no relevance to azelastine nasal spray as given recommended nasal doses result in much lower systemic exposure. Nevertheless, care should be taken when administering azelastine hydrochloride in patients taking concurrent sedative or central nervous medications because sedative effect may be enhanced. Alcohol may also enhance this effect (see section 4.7).

4.6 Fertility, pregnancy and lactation

Fertility

There are only limited data with regard to fertility (see section 5.3).

Pregnancy

There are no or limited amount of data from the use of azelastine hydrochloride and fluticasone propionate in pregnant women. Therefore, Dymista Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section 5.3)

Lactation

It is unknown whether nasally administered azelastine hydrochloride/metabolites or fluticasone propionate/metabolites are excreted in human breast milk. Dymista Nasal Spray should be used during lactation only if the potential benefit justifies the potential risk to the newborns/infant (see section 5.3).

4.7 Effects on ability to drive and use machines

Dymista Nasal Spray has minor influence on the ability to drive and use machines.

In isolated cases fatigue, weariness, exhaustion, dizziness or weakness that may also be caused by the disease itself, may occur when using Dymista Nasal Spray. In these cases, the ability to drive and use machines may be impaired. Alcohol may enhance this effect.

4.8 Undesirable effects

Commonly, dysgeusia, a substance-specific unpleasant taste, may be experienced after administration (often due to incorrect method of application, namely tilting the head too far backwards during administration).

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

Frequency	***Very common***	***Common***	***Uncommon***	***Rare***	***Very rare***	***Not known***
System Organ						

Class						
Immune system disorders					Hypersensitivity including anaphylactic reactions, angioedema (oedema of the face or tongue and skin rash), bronchospasm	
Nervous system disorder		Headache, Dysgeusia (unpleasant taste), unpleasant smell			Dizziness, somnolence (drowsiness, sleepiness)	
Eye disorders*					Glaucoma, increased intraocular pressure, cataract	Vision, blurred (see also section 4.4)
Respiratory, thoracic and mediastinal disorders	Epistaxis		Nasal discomfort (including nasal irritation, stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation		Nasal septal perforation**, mucosal erosion	Nasal ulcers
Gastrointestinal disorders				Dry mouth	Nausea	
Skin and subcutaneous tissue disorders					Rash, pruritus, urticaria	
General disorders and administration site conditions					Fatigue (weariness, exhaustion), weakness (see section 4.7)	

***** A very small number of spontaneous reports have been identified following prolonged treatment with intranasal fluticasone propionate.

** Nasal septal perforation has been reported following the use of intranasal corticosteroids.

Systemic effects of some nasal corticosteroids may occur, particularly when administered at high doses for prolonged periods (see section 4.4).

Growth retardation has been reported in children receiving nasal corticosteroids. Growth retardation may be possible in adolescents, too (see section 4.4).

In rare cases osteoporosis was observed, if nasal glucocorticoids were administered long-term.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

With the nasal route of administration overdose reactions are not anticipated.

There are no data from patients available on the effects of acute or chronic overdosage with intranasal fluticasone propionate.

Intranasal administration of 2 milligrams fluticasone propionate (10 times the recommended daily dose) twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.

Administration of doses higher than those recommended over a long period of time may lead to temporary suppression of adrenal function.

In these patients, treatment with Dymista Nasal Spray should be continued at a dose sufficient to control symptoms; the adrenal function will recover in a few days and can be verified by measuring plasma cortisol.

In the event of overdose after incidental oral uptake, disturbances of the central nervous system (including drowsiness, confusion, coma, tachycardia and hypotension) caused by azelastine hydrochloride are to be expected based on the results of animal experiments.

Treatment of these disorders must be symptomatic. Depending on the amount swallowed, gastric lavage is recommended. There is no known antidote.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use, corticosteroids/ fluticasone, combinations, ATC code: R01AD58.

Mechanism of action and pharmacodynamic effects

Dymista Nasal Spray contains azelastine hydrochloride and fluticasone propionate, which have different modes of action and show synergistic effects in terms of improvement of allergic rhinitis and rhino-conjunctivitis symptoms.

Fluticasone propionate

Fluticasone propionate is a synthetic trifluorinated corticosteroid that possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action, e.g. 3-5 fold more potent than dexamethasone in cloned human glucocorticoid receptor binding and gene expression assays.

Azelastine hydrochloride

Azelastine, a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H_1-antagonist, mast cell stabilizing and anti-inflammatory properties. Data from *in vivo* (preclinical) and *in vitro* studies show that azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late stage allergic reactions, e.g. leukotrienes, histamine, platelet-activating factor (PAF) and serotonin.

. A relief of nasal allergic symptoms is observed within 15 minutes after administration.

Dymista Nasal Spray

In 4 clinical studies in adults and adolescents with allergic rhinitis Dymista Nasal Spray one spray in each nostril twice daily significantly improved nasal symptoms (comprising rhinorrhoea, nasal congestion, sneezing and nasal itching) compared with placebo, azelastine hydrochloride alone and fluticasone propionate alone. It significantly improved ocular symptoms (comprising itching, tearing/watering and redness of the eyes) and the patients' disease-related quality of life (Rhinoconjunctivitis Quality of Life Questionnaire – RQLQ) in all 4 studies.

In comparison to a marketed fluticasone propionate nasal spray substantial symptom improvement (50% reduction in nasal symptoms severity) was achieved significantly earlier (3 days and more) with Dymista Nasal Spray. The superior effect of Dymista Nasal Spray to fluticasone propionate nasal spray was maintained throughout one-year study in patients with chronic persistent allergic rhinitis and nonallergic/vasomotor rhinitis.

5.2 Pharmacokinetic properties

Absorption

After intranasal administration of two sprays per nostril (548 mcg of azelastine hydrochloride and 200 mcg of fluticasone) of Dymista Nasal Spray, the mean (± standard deviation) peak plasma exposure (C_{max}) was 194.5 ± 74.4 pg/mL for azelastine and 10.3 ± 3.9 pg/mL for fluticasone propionate and the mean total exposure (AUC) was 4217 ± 2618 pg/mL*hr for azelastine and 97.7 ± 43.1 pg/mL*hr for fluticasone. The median time to peak exposure (t_{max}) from a single dose was 0.5 hours for azelastine and 1.0 hours for fluticasone.

Fluticasone systemic exposure was ~50% increased comparing Dymista Nasal Spray with a marketed fluticasone nasal spray. Dymista Nasal Spray was equivalent to a marketed azelastine nasal spray with respect to azelastine systemic exposure. There was no evidence of pharmacokinetic interactions between azelastine hydrochloride and fluticasone propionate.

Distribution

Fluticasone propionate has a large volume of distribution at steady-state (approximately 318 litre). Plasma protein binding is 91%.

The volume of distribution of azelastine is high indicating distribution predominantly into the peripheral tissue. The level of protein binding is 80-90%. Additionally, both drugs have broad therapeutic windows. Therefore, drug displacement reactions are unlikely.

Biotransformation

Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Azelastine is metabolized to *N*-desmethylazelastine via various CYP isoenzymes, mainly CYP3A4, CYP2D6 and CYP2C19.

Elimination

The elimination rate of intravenous administered fluticasone propionate is linear over the 250—1000 microgram dose range and are characterised by a high plasma clearance (CL=1.1 l/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8 h terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

Plasma elimination half-lives after a single dose of azelastine are approximately 20-25 hours for azelastine and about 45 hours for the therapeutically active metabolite *N*-desmethylazelastine. Excretion occurs mainly via the faeces. The sustained excretion of small amounts of the dose in the faeces suggests that some enterohepatic circulation may take place.

5.3 Preclinical safety data

Fluticasone propionate

Findings in general toxicology studies were similar to those observed with other glucocorticoids and are associated with exaggerated pharmacological activity. These findings are not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure. No genotoxic effects of fluticasone propionate have been observed in conventional genotoxicity tests. Further, there were no treatment-related increases in the incidence of tumours in two year inhalation studies in rats and mice.

In animal studies glucocorticoids have been shown to induce malformations including cleft palate and intra-uterine growth retardation. Again this is not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure (see section 5.2).

Azelastine hydrochloride

Azelastine hydrochloride displayed no sensitising potential in the guinea pig. Azelastine demonstrated no genotoxic potential in a battery of in vitro and in vivo tests, nor any carcinogenic potential in rats or mice. In male and female rats, azelastine at oral doses greater than 3 mg/kg/day caused a dose-related decrease in the fertility index; no substance-related alterations were found in the reproductive organs of males or females during chronic toxicity studies, however, embryotoxic and teratogenic effects in rats, mice and rabbits occurred only at maternal toxic doses (for example, skeletal malformations were observed in rats and mice at doses of 68.6 mg/kg/day).

Dymista Nasal Spray

Repeated dose intranasal toxicity studies in rats for a period up to 90 days and in dogs for 14 days with Dymista Nasal Spray revealed no new adverse effects in comparison to the individual components.

6. Pharmaceutical particulars

6.1 List of excipients

Disodium edetate

Glycerol

Microcrystalline cellulose

Carmellose sodium

Polysorbate 80

Benzalkonium chloride

Phenylethyl alcohol

Purified water

6.2 Incompatibilities

Not applicable.

For use with question 4, *please turn over*:

DOAC dosing in non-valvular AF

Renal function	CrCL > 50 mL/min					
	Age < 75y and wt > 50 kg	Age 75-79y and wt > 50 kg	Age ≥ 80y and wt > 60 kg	Age ≥ 80y and 50 - ≤ 60 kg	HASBLED ≥3 Or ↑ bleeding risk	Any age and < 50 kg or > 120 kg
Rivaroxaban	20 mg od				Consider 15 mg od	Do not use*
Apixaban	5 mg bd			2.5 mg bd	Consider 2.5mg bd	Do not use*
Edoxaban Avoid if CrCL >95mL/min**	60 mg od 30 mg od if ≤ 60kg or if taking P-gp inhibitor e.g. ciclosporin, dronedarone, erythromycin, ketoconazole (see also drug interaction table)			30 mg od	Consider 30mg OD	Do not use*
Dabigatran	150 mg bd 110mg bd if also on verapamil OR at ↑risk of bleeding (e.g. GI risks)	110 mg bd	110 mg bd			Do not use*

* Unless specifically advised by local haematology consultant. ** ↑ rate of ischaemic stroke vs warfarin (AF)
NB: Certain drug interactions (other than those stated above / below) may also require consideration of dose reduction (see drug interaction table)
NB: Haematologist may advise individualised doses other than those detailed within these tables

Renal function	CrCL 30 - ≤ 50mL/min				Cr CL 15 - mL/min	Cr CL < 15 mL/min
	Age < 75y and wt > 50 kg	Age 75 - 79 y and wt > 50 kg	Age ≥ 80y and wt > 50 kg	Any age and wt < 50 kg or > 120 kg	Any age / wt	Any age / wt
Rivaroxaban	15 mg od			Do not use*	Do not use*	Contra-indicated
Apixaban	5mg bd if > 60 kg 2.5mg bd if 50 - ≤ 60kg (consider 2.5mg bd if HASBLED ≥3 OR at ↑risk of bleeding)		2.5mg bd	Do not use*	Do not use*	
Edoxaban	30 mg od			Do not use*	Do not use*	
Dabigatran	150 mg bd 110 mg bd if OR at ↑risk of bleeding ≥3 or	110 mg bd	Consider alternative drug	Do not use*	Contra-indicated	

Cockcroft & Gault (C&G) formula

- eGFR and calculated CrCL are NOT interchangeable, but in practice and for most adult patients of average build and height, eGFR can be used to determine dosing in place of CrCL
- Calculated CrCL rather than eGFR should be used (with caution) in the following patient populations:
  - the elderly
  - reduced muscle mass
  - poor nutritional status
  - BMI <18.5 or >30
  - eGFR ≤50mL/min

Example of electronic CrCL (C&G) calculator

http://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation/

$$\text{CrCL (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times \text{constant}}{\text{serum creatinine (µmol/L)}}$$

- Constant = 1.23 (male) or 1.04 (female)
- Weight (kg) = **current weight** or **adjusted body weight** (ABW) if obese*

  *Obese defined as >20% over ideal bodyweight (IBW) (see table)
- **Adjusted body weight (ABW)** =
  Ideal body weight + 0.4 (current body weight - ideal body weight)

HEIGHT		IDEAL BODY WEIGHT (kg)	
feet	cm	Male	Female
5ft 1in	155	52.3	47.8
5ft 2in	158	54.6	50.1
5ft 3in	160	56.9	52.4
5ft 4in	163	59.2	54.7
5ft 5in	165	61.5	57.0
5ft 6in	168	63.8	59.3
5ft 7in	170	66.1	61.6
5ft 8in	173	68.4	63.9
5ft 9in	175	70.7	66.2
5ft 10	178	73.0	68.5
5ft 11	180	75.3	70.8
6ft	183	77.6	73.1
6ft 1in	185	79.9	75.4
6ft 2in	188	82.2	77.7

For use with question 9:

FOSPHENYTOIN SODIUM

Drug action

Fosphenytoin is a pro-drug of phenytoin.

Indications and dose

Status epilepticus

By intravenous infusion

For Adult
Initially 20 mg(PE)/kg, dose to be administered at a rate of 100–150 mg(PE)/minute, then 4–5 mg(PE)/kg daily in 1–2 divided doses, dose to be administered at a rate of 50–100 mg(PE)/minute, dose to be adjusted according to response and trough plasma-phenytoin concentration.

For Elderly
Consider 10–25% reduction in dose or infusion rate.

Prophylaxis or treatment of seizures associated with neurosurgery or head injury

By intramuscular injection, or by intravenous infusion

For Adult
Initially 10–15 mg(PE)/kg, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute, then 4–5 mg(PE)/kg daily in 1–2 divided doses, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute, dose to be adjusted according to response and trough plasma-phenytoin concentration.

For Elderly
Consider 10–25% reduction in dose or infusion rate.

Temporary substitution for oral phenytoin

By intramuscular injection, or by intravenous infusion

For Adult
Same dose and same dosing frequency as oral phenytoin therapy, intravenous infusion to be administered at a rate of 50–100 mg(PE)/minute.

For Elderly
Consider 10–25% reduction in dose or infusion rate.

Dose equivalence and conversion

Doses are expressed as phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg ≡ phenytoin sodium 1 mg.

Solution for injection All products

Electrolytes

May contain

Phosphate

Pro-Epanutin 750mg/10ml concentrate for solution for injection vials (Pfizer Ltd)

Active ingredients	Size	Unit	NHS indicative price	Drug tariff	Drug tariff price
• Fosphenytoin sodium 75 mg per 1 ml	10	vial (POM)	£400.00 (Hospital only)	—	—

For use with question 17, *please turn over*:

Gaviscon Original Aniseed Relief

Summary of Product Characteristics Updated 19-Sep-2019 | Reckitt Benckiser Healthcare (UK) Ltd

1. Name of the medicinal product

Gaviscon Original Aniseed Relief.

2. Qualitative and quantitative composition

Gaviscon Original Aniseed Relief contains 250 mg sodium alginate, 133.5 mg sodium bicarbonate and 80 mg calcium carbonate per 5 ml.

Excipient(s) with known effect:

Methyl parahydroxybenzoate E218

Propyl parahydroxybenzoate E216

Benzyl alcohol

Sodium

For excipients, see Section 6.1.

3. Pharmaceutical form

Oral suspension.

An opaque, pink suspension with the odour and flavour of fennel.

4. Clinical particulars

4.1 Therapeutic indications

Gastric reflux, heartburn, flatulence associated with gastric reflux, heartburn of pregnancy, all cases of epigastric and retrosternal distress where the underlying cause is gastric reflux.

4.2 Posology and method of administration

For oral administration.

Adults and children over 12 years: 10-20ml after meals and at bedtime.

Children under 12 years: Should be given only on medical advice.

Elderly: No dosage modification is required in this age group.

Hepatic Impairment: No dose modification necessary.

Renal Insufficiency: Caution if highly restricted salt diet is necessary (see section 4.4).

4.3 Contraindications

This medicinal product is contraindicated in patients with known or suspected hypersensitivity to the active substances or to any of the excipients listed in section 6.1, including methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) (see section 4.4).

4.4 Special warnings and precautions for use

If symptoms do not improve after 7 days, the clinical situation should be reviewed.

This medicinal product contains 285.2 mg (12.4 mmol) sodium per 20 ml dose, equivalent to 14.26 % of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 57% of the WHO recommended maximum daily intake for sodium.

This product is considered high in sodium. This should be particularly taken into account for those on a low salt diet (e.g. in some cases of congestive heart failure and renal impairment).

Each 10 ml dose contains 160 mg (1.6 mmol) of calcium carbonate. Care needs to be taken in treating patients with hypercalcaemia, nephrocalcinosis and recurrent calcium containing renal calculi.

Contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

This medicine contains 2.2 mg benzyl alcohol (from Fennel flavour) per 20 ml dose. Benzyl alcohol may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

A time-interval of 2 hours should be considered between Gaviscon intake and the administration of other medicinal products, especially tetracyclines, digoxine, fluoroquinolone, iron salt, ketoconazole, neuroleptics, thyroid hormones, penicillamine, beta-blockers (atenolol, metoprolol, propanolol), glucocorticoid, chloroquine and biphosphonates (diphosphonates) and estramustine. See also 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Clinical studies in more than 500 pregnant women as well as a large amount of data from post-marketing experience indicate no malformative nor feto/ neonatal toxicity of the active substances.

Gaviscon can be used during pregnancy, if clinically needed.

Breast feeding:

No effects of the active substances have been shown in breastfed newborns/infants of treated mothers. Gaviscon can be used during breast-feeding.

Fertility:

Pre-clinical investigations have revealed alginate has no negative effect on parental or offspring fertility or reproduction.

Clinical data do not suggest that Gaviscon has an effect on human fertility.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Adverse reactions have been ranked under headings of frequency using the following convention: very common (1/10), common (1/100 and <1/10), uncommon (1/1000 and <1/100), rare (1/10,000 and <1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Event
Immune System Disorders	Very rare	Anaphylactic and anaphylactoid reactions. Hypersensitivity reactions such as urticaria.
Respiratory, Thoracic and Mediastinal Disorders	Very rare	Respiratory effects such as bronchospasm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Symptoms are likely to be minor; some abdominal discomfort may be experienced.

Management

In the event of overdose symptomatic treatment should be given.

5. Pharmacological properties

5.1 Pharmacodynamic properties

On ingestion the product reacts rapidly with gastric acid to form a raft of alginic acid gel having a near neutral pH and which floats on the stomach contents, **quickly and** effectively impeding gastro-oesophageal reflux**, for up to 4 hours**. In severe cases the raft itself may be refluxed into the oesophagus, in preference to the stomach contents, and exert a demulcent effect.

5.2 Pharmacokinetic properties

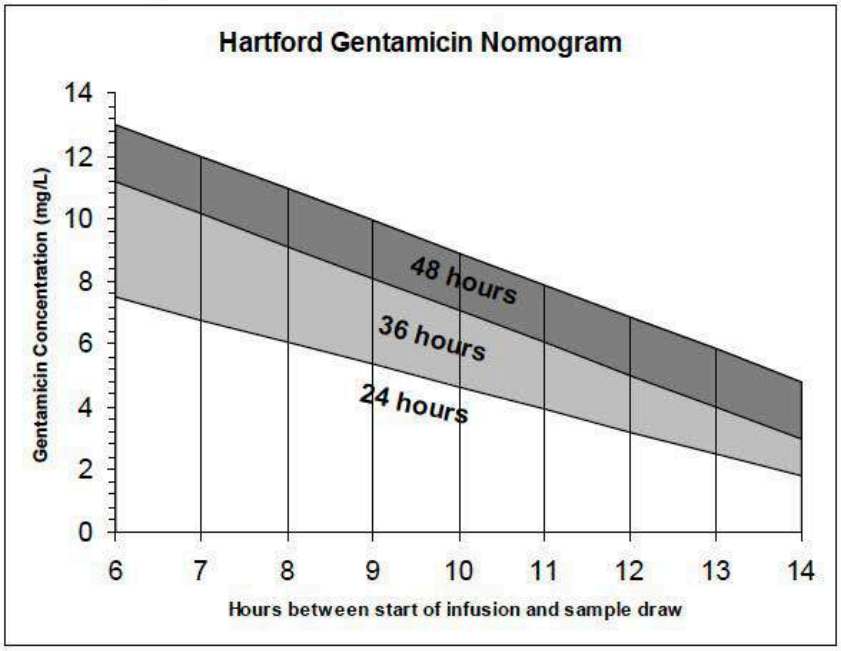
The mode of action of the product is physical and does not depend on absorption into the systemic circulation.

5.3 Preclinical safety data

No preclinical findings relevant to the prescriber have been reported.

For use with question 27:

Monitoring



- Take a 10mL blood sample 6 – 14 hours after the 1st infusion (Do not take the sample from the same line used for gentamicin administration).
- Document on the microbiology request the EXACT time and date the infusion was set up and the EXACT time and date the sample was taken.
- Record the resulting level on the nomogram.
- If the level falls in the area designated 24hours, 36hours or 48hours, the dosing interval is 24, 36 or 48 hourly respectively.
- If the level is above the 48 hour line then STOP the treatment. If gentamicin is to be continued take daily levels, but do not give any more gentamicin until the level falls below 2mg/L.
- Check U & E's and creatinine daily to monitor renal function.
- Gentamicin may be reported in micrograms/mL rather than mg/L. These units are equivalent.

Dosage Interval	Repeat levels every	
24 hours	3 days	(on every third dose)
36 hours	3 days	(on alternate doses)
48 hours	2 days	(on each dose)

Refer to the full Yorkshire Hartford Gentamicin Regimen (available in Pharmacy) for further information if required.

Adapted from Bradford Hospitals Gentamicin Chart

[1] Gentamicin can be given in 50mL sodium chloride 0.9% if the patient is fluid restricted.

For use with question 31, *please turn over*:

COAL TAR WITH SALICYLIC ACID AND PRECIPITATED SULFUR

Indications and dose

For Sebco® ointment

Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

To the skin using scalp ointment

For Child 6–11 years
Medical supervision required.

For Child 12–17 years
Apply as required, alternatively apply daily for the first 3–7 days (if severe), shampoo off after 1 hour.

For Adult
Apply as required, alternatively apply daily for the first 3–7 days (if severe), shampoo off after 1 hour.

For Cocois® ointment

Scaly scalp disorders including psoriasis, eczema, seborrhoeic dermatitis and dandruff

Initially to the skin using scalp ointment

For Child 6–11 years
Medical supervision required.

For Child 12–17 years
Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour.

For Adult
Apply once weekly as required, alternatively (to the skin) apply daily for the first 3–7 days (if severe), shampoo off after 1 hour.

Excipients

May contain

Cetostearyl alcohol (including cetyl and stearyl alcohol)

Cocois ointment (RPH Pharmaceuticals AB)

Active ingredients	Size	Unit	NHS indicative price	Drug tariff	Drug tariff price
• Coal tar solution 120 mg per 1 gram • Salicylic acid 20 mg per 1 gram • Sulfur precipitated 40 mg per 1 gram	40	gram (GSL)	£6.22	—	—
	100	gram (GSL)	£11.69	—	—

Sebco ointment (Derma UK Ltd)

Active ingredients	Size	Unit	NHS indicative price	Drug tariff	Drug tariff price
• Coal tar solution 120 mg per 1 gram • Salicylic acid 20 mg per 1 gram • Sulfur precipitated 40 mg per 1 gram	40	gram (GSL)	£7.91	—	—
	100	gram (GSL)	£13.38	—	—

Phenoxymethyl Penicillin 250mg/5ml Oral Solution Sugar Free (syringe)

Summary of Product Characteristics Updated 29-Aug-2017 | Kent Pharmaceuticals Ltd

1. Name of the medicinal product

Phenoxymethylpenicillin 250mg/5ml Oral Solution Sugar Free BP

2. Qualitative and quantitative composition

Each 5ml of Oral Solution contains 250mg of Phenoxymethylpenicillin as Phenoxymethylpenicillin Potassium Ph. Eur.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Powder for oral solution

4. Clinical particulars

4.1 Therapeutic indications

Phenoxymethylpenicillin and phenoxymethylpenicillin potassium are indicated in the treatment of mild to moderately severe infections associated with micro-organisms whose susceptibility to penicillin is within the range of serum levels attained with the dosage form.

Phenoxymethylpenicillin is indicated for the treatment of the following infections (see section 4.4 and 5.1)

Streptococcal infections:

Pharyngitis

Scarlet fever

Skin and soft tissue infections (e.g erysipelas)

Pneumococcal infections:

Pneumonia

Otitis media

Vincent's gingivitis and pharyngitis

Phenoxymethylpenicillin is also indicated for (see section 5.1):

Prophylaxis of rheumatic fever and/or chorea

Prophylaxis of pneumococcal infection (e.g. in asplenia and inpatients with sickle cell disease

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

For oral administration only

The dosage and frequency of Phenoxymethylpenicillin depends on the severity and localisation of the infection and expected pathogens.

Phenoxymethylpenicillin Solution should be taken at least 30 minutes before or 2 hours after food, as ingestion of Phenoxymethylpenicillin with meals slightly reduces the absorption of the drug.

Phenoxymethylpenicillin 250mg is approximately equivalent to 400,000 units.

The usual dosage recommendations are as follows:

Adults and children over 12 years: 250mg - 500mg every six hours

Children: Infants (up to 1 year): 62.5mg every 6 hours

1-5 years: 125mg every six hours

6-12 years: 250mg every six hours

Prophylactic Use

Prophylaxis of rheumatic fever/chorea: 250mg twice daily on a continuing basis

Prophylaxis of pneumococcal infection (e.g. in asplenia and in sickle cell disease):

Adults and children over 12 years: 500mg every 12 hours

Children 6-12 years: 250mg every 12 hours

Children below 5 years: 125mg every 12 hours.

Elderly

The dosage is as for adults. The dosage should be reduced if renal function is markedly impaired.

Renal impairment

The dosage should be reduced if renal function is markedly impaired.

Hepatic impairment

Dosage adjustment may be necessary in patients with impaired liver function when they also have renal failure. In this situation the liver may be a major excretion route.

Method of Administration

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

Phenoxymethylpenicillin is contraindicated in patients known to be hypersensitive to Penicillin and should be used with caution in patients with known histories of allergy.

Sorbitol:

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.4 Special warnings and precautions for use

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

All degrees of hypersensitivity, including fatal anaphylaxis, have been observed with oral penicillin. These reactions are more likely to occur in individuals with a history of sensitivity to penicillins, cephalosporins and other allergens. Enquiries should be made for such a history before therapy is begun. If any allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. adrenaline and other pressor amines, antihistamines and corticosteroids).

Oral therapy should not be relied upon for patients with severe illness, or with nausea, vomiting, gastric dilation, achalasia or intestinal hypermotility. Occasionally patients do not absorb therapeutic amounts of orally administered penicillin.

Administer with caution in the presence of markedly impaired renal function, as safe dosage may be lower than the usually recommended doses.

Streptococcal infections should be treated for a minimum of 10 days, and post therapy cultures should be performed to confirm the eradication of the organisms.

Prolonged use of antibiotics may promote the over growth of non-susceptible organisms, including fungi. If super infection occurs, appropriate measures should be taken.

Severe empyema, bacteraemia, pericarditis, meningitis and arthritis should not be treated with Penicillin V during the acute phase.

Patients with a past history of rheumatic fever receiving continuous prophylaxis may harbour penicillin-resistant organisms. In these patients, the use of another prophylactic agent should be considered.

Oral penicillin should not be used as adjunctive prophylaxis for genito - urinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy and child birth.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycosides: Neomycin is reported to reduce the absorption of phenoxymethylpenicillin.

Anticoagulants: Penicillins may interfere with anticoagulant control.

Bacteriostatic antibiotics: Certain bacteriostatic antibiotics such as Chloramphenicol, Erythromycin and Tetracyclines have been reported to antagonise the bactericidal activity of penicillins and concomitant use is not recommended.

Guar gum: Reduced absorption of phenoxymethylpenicillin

Methotrexate: Use of Phenoxymethylpenicillin while taking methotrexate can cause reduced excretion of methotrexate thereby increasing the risk of toxicity.

Probenecid: Reduced excretion of phenoxymethylpenicillin by competing with it for renal tubular secretion.

Sulfinpyrazone: Excretion of penicillins reduced by sulfinpyrazone.

Typhoid vaccine (oral): Penicillins may inactivate oral typhoid vaccine if ingested concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no or a limited amount of data from the use of Phenoxymethylpenicillin in pregnant women. As a precautionary measure, it is preferable to avoid the use of Phenoxymethylpenicillin during pregnancy.

Lactation:

Phenoxymethylpenicillin metabolites are excreted in human milk to such an extent that effects on breastfed newborns are likely.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

The most common reactions to oral penicillin are gastrointestinal effects and hypersensitivity reactions. Although hypersensitivity reactions have been reported much less frequently after oral than after parenteral therapy, it should be remembered that all forms of hypersensitivity, including fatal anaphylaxis have been observed with oral penicillin.

The following convention has been utilised for the classification of undesirable effects:- Very common (≥1/10) Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100) Rare (≥1/10,000, <1/1000) Very rare (<1/10,000) Not known (cannot be estimated from the available data).		
Infections and infestations	Not known	Pseudomembranous colitis
Blood and lymphatic disorders	Very rare	Changes in blood counts, including, thrombocytopenia, neutropenia, leucopenia, eosinophilia and haemolytic anaemia.
	Not known	Coagulation disorders (including prolongation of bleeding time and defective platelet function)
Gastrointestinal disorders	Common	Nausea, vomiting, abdominal pain, diarrhoea
	Not known	Sore mouth and black hairy tongue (discolouration of tongue)
Hepatobiliary disorders	Very rare	Hepatitis and cholestatic jaundice
Immune disorders	Common	Allergic reactions (typically manifest as skin reactions (See Skin and subcutaneous disorders)).
	Rare	Severe allergic reactions causing angioedema, laryngeal oedema and anaphylaxis
	Unknown	Serum sickness-like reactions characterised by fever, chills, arthralgia and oedema
Nervous system disorders	Unknown	Central nervous system toxicity including convulsions (especially with high doses or in severe renal impairment); paraesthesia may occur with prolonged use, Neuropathy (usually associated with high doses of parenteral penicillin)
Renal and urinary disorders	Very rare	Interstitial nephritis
	Uncommon	Nephropathy (usually associated with high doses of parenteral penicillin)
Skin and subcutaneous disorders	Common	Urticarial, erythematous or mobilliform rash and pruritus

	Rare	Exfoliative dermatitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the yellow card scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms**:** A large oral overdose of penicillin may cause nausea, vomiting, stomach pain, diarrhoea, and rarely, major motor seizures. If other symptoms are present, consider the possibility of an allergic reaction. Hyperkalaemia may result from overdosage, particularly for patients with renal insufficiency.

Management: No specific antidote is known. Symptomatic and supportive therapy is recommended. Activated charcoal with a cathartic, such as sorbitol may hasten drug elimination. Penicillin may be removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: J01CE02

Phenoxymethylpenicillin is abeta-lactamase sensitive natural penicillin.

Mechanism of Action:

Phenoxymethylpenicillin acts through interference with the final stage of synthesis of the bacterial cell wall. The action depends on its ability to bind certain membrane-bound proteins, (penicillin-binding proteins or PBPs) that are located beneath the cell wall. These proteins are involved in maintaining cell wall structure, in cell wall synthesis and in cell division, and appear to possess transpeptidase and carboxypeptidase activity.

PK/PD relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for phenoxymethylpenicillin.

Mechanism(s) of Resistance:

Phenoxymethylpenicillin is inhibited by penicillinase and other beta-lactamases that are produced by certain micro-organisms. The incidence of beta-lactamase producing organisms is increasing.

Mechanisms of resistance

The two main mechanisms of resistance to phenoxymethylpenicillin are:

• Inactivation by bacterial penicillinases and other beta-lactamases

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance.

EUCAST clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens (version 1.0 22.11.210) are:

The susceptibility of streptococci Groups A, C and G and *S. pneumoniae* to phenoxymethylpenicillin is inferred from the susceptibility to benzylpenicillin.

EUCAST Species-related breakpoints (Susceptible≤/Resistant>) Units: mg/L	
Staphylococcus	≤0.12/>0.12
Streptococcus A, C, G	≤0.25/>*0.25*
S. pneumoniae	≤ 0.06/>2

Staphylococci: Most staphylococci are penicillinase-producers. Penicillinase-producing strains are resistant. The benzylpenicillin breakpoint (shown) will mostly, but not unequivocally, separate beta-lactamase producers from non-producers.

***Streptococcus pneumoniae*:** For phenoxymethylpenicillin, report *S. pneumoniae* with benzylpenicillin MICs above 0.06 mg/L resistant.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Expert advice should be sought as necessary when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable.

Commonly susceptible species
Streptococcus A, C, G
Species for which acquired resistance may be a problem
Staphylococcus aureus
Streptococcus pneumoniae
Staphylococcus epidermidis

5.2 Pharmacokinetic properties

Absorption: Rapidly but incompletely absorbed after oral administration (about 60% of an oral dose is absorbed). Calcium and potassium salts are better absorbed than the free acid. Absorption appears to be reduced in patients with coeliac disease. Absorption appears to be more rapid in fasting than non-fasting subjects.

Blood concentration: after an oral dose of 125mg, peak serum concentrations of 200 to 700ng/ml are attained in 2 hours. After an oral dose of 500mg, peak serum concentrations reach 3 to 5micrograms/ml in 30 to 60 minutes.

Half-life: Biological half-life is about 30 minutes, increased to about 4 hours in severe renal impairment.

Distribution: Widely distributed throughout the body and enters pleural and ascitic fluids and also in cerebrospinal fluid when the meninges are inflamed; Phenoxymethylpenicillin crosses the placenta and is secreted in trace amounts in breast milk; (protein binding 50% to 80% bound plasma proteins).

Biotransformation: It is metabolised in the liver; several metabolites have been identified, including penicilloic acid.

Elimination: Unchanged drug and metabolites are excreted rapidly in the urine. (20% to 35% of an oral dose is excreted in the urine in 24 hours).

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of this SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Benzoate Ph. Eur.

Saccharin Sodium Ph. Eur.

Trusil Orange Flavour HSE

Orange Colour 175 78 8 HSE

(Containing sunset yellow E110 & Ponceau 4R E124)

Sorbitol 60W

Mono Ammonium Glycyrrhizinate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened container: 24 months

Reconstituted oral solution: a shelf life of 7 days

6.4 Special precautions for storage

Unconstituted powder: Store in a dry place below 25°C. Protect from light

Reconstituted oral solution: Store for 7 days in a refrigerator (2 °C - 8 °C).

6.5 Nature and contents of container

Natural high density polyethylene bottle 150ml with white cap with a blue TE band containing 100ml of oral solution on reconstitution.

For use with question 40:

Buprenorphine patches are *approximately* equivalent to the following 24-hour doses of oral morphine

morphine salt 12 mg daily	≡ buprenorphine '5' patch
morphine salt 24 mg daily	≡ buprenorphine '10' patch
morphine salt 36 mg daily	≡ buprenorphine '15' patch
morphine salt 48 mg daily	≡ buprenorphine '20' patch
morphine salt 84 mg daily	≡ buprenorphine '35' patch
morphine salt 126 mg daily	≡ buprenorphine '52.5' patch
morphine salt 168 mg daily	≡ buprenorphine '70' patch

Formulations of transdermal patches are available as 72-hourly, 96-hourly and 7-day patches, for further information see buprenorphine. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

72-hour Fentanyl patches are *approximately* equivalent to the following 24-hour doses of oral morphine

morphine salt 30 mg daily	≡ fentanyl '12' patch
morphine salt 60 mg daily	≡ fentanyl '25' patch
morphine salt 120 mg daily	≡ fentanyl '50' patch
morphine salt 180 mg daily	≡ fentanyl '75' patch
morphine salt 240 mg daily	≡ fentanyl '100' patch

Fentanyl equivalences in this table are for patients on well-tolerated opioid therapy for long periods; for patients who are opioid naive or who have been stable on oral morphine or other immediate release opioid for only several weeks, see Transdermal Route. Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.