KING'S MOCK REGISTRATION ASSESSMENT 2020 PART 2 RESOURCE PACK

Instructions to candidates

1. This resource pack is available to use for questions; 7, 8, 10, 11, 13, 15, 18, 21, 24, 33, 36, 37, 39, 41 and 44.
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 questions 7 & 8, *please turn over*:

Byetta 5 micrograms solution for injection, prefilled pen. Byetta 10 micrograms solution for injection, prefilled pen.

Summary of Product Characteristics Updated 11-Jan-2016 | AstraZeneca UK Limited

1. Name of the medicinal product

BYETTA 5 micrograms solution for injection, prefilled pen

BYETTA 10 micrograms solution for injection, prefilled pen

2. Qualitative and quantitative composition

Each dose contains 5 micrograms (mcg) exenatide in 20 microlitres(mcl), (0.25 mg exenatide per ml).

Excipients:

Each dose contains 44 mcg metacresol.

Each dose contains 10 micrograms (mcg) exenatide in 40 microlitres(mcl), (0.25 mg exenatide per ml).

Excipients:

Each 10 mcg dose contains 88 mcg metacresol.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection (injection), pre-filled pen.

Clear, colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

BYETTA is indicated for treatment of type 2 diabetes mellitus in combination with:

- metformin
- sulphonylureas
- thiazolidinediones
- metformin and a sulphonylurea
- metformin and a thiazolidinedione

in adults who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.

BYETTA is also indicated as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.

4.2 Posology and method of administration

Posology

BYETTA therapy should be initiated at 5 mcg exenatide per dose administered twice daily (BID) for at least one month in order to improve tolerability. The dose of exenatide can then be increased to 10 mcg BID to further improve glycaemic control. Doses higher than 10 mcg BID are not recommended.

BYETTA is available as either a 5 mcg or a 10 mcg exenatide per dose pre-filled pen.

BYETTA can be administered at any time within the 60-minute period before the morning and evening meal (or two main meals of the day, approximately 6 hours or more apart). BYETTA **should not** be administered after a meal. If an injection is missed, the treatment should be continued with the next scheduled dose.

BYETTA is recommended for use in patients with type 2 diabetes mellitus who are already receiving metformin, a sulphonylurea, pioglitazone and/or a basal insulin. One can continue to use BYETTA when a basal insulin is added to existing therapy. When BYETTA is added to existing metformin and/or pioglitazone therapy, the current dose of metformin and/or pioglitazone can be continued as no increased risk of hypoglycaemia is anticipated, compared to metformin or pioglitazone alone. When BYETTA is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia (see section 4.4.). When BYETTA is used in combination with basal insulin, the dose of basal insulin should be evaluated. In patients at increased risk of hypoglycaemia consider reducing the dose of basal insulin (see section 4.8).

The dose of BYETTA does not need to be adjusted on a day-by-day basis depending on self-monitored glycaemia. However, blood glucose self-monitoring may become necessary to adjust the dose of sulphonylureas or the dose of basal insulin.

Special populations

Elderly

BYETTA should be used with caution and dose escalation from 5 mcg to 10 mcg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very limited.

Renal impairment

No dosage adjustment of BYETTA is necessary in patients with mild renal impairment (creatinine clearance 50 – 80 ml/min).

In patients with moderate renal impairment (creatinine clearance 30-50 ml/min), dose escalation from 5 mcg to 10 mcg should proceed conservatively (see section 5.2).

BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

Hepatic impairment

No dosage adjustment of BYETTA is necessary in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and effectiveness of exenatide have not been established in patients under 18 years of age (see section 5.2).

Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

Each dose should be administered as a subcutaneous injection in the thigh, abdomen, or upper arm.

BYETTA and basal insulin must be administered as two separate injections.

For instructions for using the pen, see section 6.6 and the instructions included with the leaflet.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

BYETTA should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

BYETTA must not be administered by intravenous or intramuscular injection.

Renal impairment

In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg increased frequency and severity of gastrointestinal adverse reactions. BYETTA is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 ml/min). The clinical experience in patients with moderate renal impairment is very limited (see section 4.2).

There have been uncommon, spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis. Some of these events occurred in patients experiencing events that may affect hydration, including nausea, vomiting, and/or diarrhoea and/or receiving medicinal products known to affect renal function/hydration status. Concomitant medicinal products included angiotensin converting enzymes inhibitors, angiotensin-II antagonists, nonsteroidal anti-inflammatory medicinal products and diuretics. Reversibility of altered renal function has been observed with supportive treatment and discontinuation of potentially causative medicinal products, including BYETTA.

Severe gastrointestinal disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Its use is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhoea. Therefore, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

Acute pancreatitis

Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been spontaneously reported events of acute pancreatitis with BYETTA. Resolution of pancreatitis has been observed with supportive treatment but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, BYETTA should be discontinued; if acute pancreatitis is confirmed, BYETTA should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Concomitant medicinal products

The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. BYETTA should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption and medicinal products with a narrow therapeutic ratio. Specific recommendations regarding intake of such medicinal products in relation to BYETTA is given in section 4.5.

The concurrent use of BYETTA with D-phenylalanine derivatives (meglitinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists has not been studied and cannot be recommended.

Patients with BMI ≤25

The experience in patients with BMI ≤25 is limited.

Rapid weight loss

Weight loss greater than 1.5 kg per week has been observed in approximately 5 % of clinical trial patients treated with exenatide. Weight loss of this rate may have harmful consequences e.g. cholelithiasis.

Hypoglycaemia

When BYETTA was used in combination with a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulphonylurea. In the clinical studies patients on a sulphonylurea combination, with mild renal impairment had an increased incidence of hypoglycaemia compared to patients with normal renal function. To reduce the risk of hypoglycaemia associated with the use of a sulphonylurea, reduction in the dose of sulphonylurea should be considered.

Excipients

This medicinal product contains less than 1 mmol sodium per dose, i.e. essentially “sodium-free”.

This medicinal product contains metacresol, which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The effect of BYETTA to slow gastric emptying may reduce the extent and rate of absorption of orally administered medicinal products. Patients receiving medicinal products of either a narrow therapeutic ratio or medicinal products that require careful clinical monitoring should be followed closely. These medicinal products should be taken in a standardised way in relation to BYETTA injection. If such medicinal products are to be administered with food, patients should be advised to, if possible, take them with a meal when BYETTA is not administered.

For oral medicinal products that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those medicinal products at least 1 hour before BYETTA injection.

Gastroresistant formulations containing substances sensitive for degradation in the stomach, such as proton pump inhibitors, should be taken at least 1 hour before or more than 4 hours after BYETTA injection.

Digoxin, lisinopril and warfarin

A delay in t_{max} of about 2 h was observed when digoxin, lisinopril or warfarin was administered 30 min after exenatide. No clinically relevant effects on C_{max} or AUC were observed. However, since market introduction, increased INR (International Normalized Ratio) has been reported spontaneously during concomitant use of warfarin and BYETTA. INR should be closely monitored during initiation and dose increase of BYETTA therapy in patients on warfarin and/or cumarol derivatives (see section 4.8).

Metformin or sulphonylureas

BYETTA is not expected to have any clinically relevant effects on the pharmacokinetics of metformin or sulphonylureas. Hence no restriction in timing of intake of these medicinal products in relation to BYETTA injection are needed.

Paracetamol

Paracetamol was used as a model medicinal product to evaluate the effect of exenatide on gastric emptying. When 1000 mg paracetamol was given with 10 mcg BYETTA (0 h) and 1 h, 2 h and 4 h after BYETTA injection, paracetamol AUCs were decreased by 21 %, 23 %, 24 % and 14 % respectively; C_{max} was decreased by 37 %, 56 %, 54 % and 41 %, respectively; t_{max} was increased from 0.6 h in the control period to 0.9 h, 4.2 h, 3.3 h, and 1.6 h, respectively. Paracetamol AUC, C_{max} and t_{max} were not significantly changed when paracetamol was given 1 hour before BYETTA injection. No adjustment to paracetamol dosing is required based on these study results.

Hydroxy Methyl Glutaryl Coenzyme A (HMG CoA) reductase inhibitors

Lovastatin AUC and C_{max} were decreased approximately 40 % and 28 %, respectively, and t_{max} was delayed about 4 h when BYETTA (10 mcg BID) was administered concomitantly with a single dose of lovastatin (40 mg) compared with lovastatin administered alone. In the 30-week placebo-controlled clinical trials, concomitant use of BYETTA and HMG CoA reductase inhibitors was not associated with consistent changes in lipid profiles (see section 5.1). Although no predetermined dose adjustment is required, one should be aware of possible changes in LDL-C or total cholesterol. Lipid profiles should be monitored regularly.

Byetta 5 micrograms solution for injection, prefilled pen. Byetta ... http://www.medicines.org.uk/emc/print-document?documentId=...

Ethinyl estradiol and levonorgestrel

Administration of a combination oral contraceptive (30 mcg ethinyl estradiol plus 150 mcg levonorgestrel) one hour before BYETTA (10 mcg BID) did not alter the AUC, C_{max} or C_{min} of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 30 minutes after BYETTA did not affect AUC but resulted in a reduction of the C_{max} of ethinyl estradiol by 45 %, and C_{max} of levonorgestrel by 27-41 %, and a delay in t_{max} by 2-4 h due to delayed gastric emptying. The reduction in C_{max} is of limited clinical relevance and no adjustment of dosing of oral contraceptives is required.

Paediatric Population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If a patient wishes to become pregnant, or pregnancy occurs, treatment with BYETTA should be discontinued.

Pregnancy

There are no adequate data from the use of BYETTA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. BYETTA should not be used during pregnancy and the use of insulin is recommended.

Breast-feeding

It is unknown whether exenatide is excreted in human milk. BYETTA should not be used if breast-feeding.

Fertility

No fertility studies in humans have been conducted.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When BYETTA is used in combination with a sulphonylurea or a basal insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions were mainly gastrointestinal related (nausea, vomiting and diarrhoea). The most frequently reported single adverse reaction was nausea which was associated with the initiation of treatment and decreased over time. Patients may experience hypoglycaemia when BYETTA is used with a sulphonylurea. Most adverse reactions associated with BYETTA were mild to moderate in intensity.

Since exenatide twice daily has been marketed, acute pancreatitis has been reported with a frequency not known and acute renal failure has been reported uncommonly (see section 4.4).

Tabulated list of adverse reactions

Table 1 lists adverse reactions reported of BYETTA from clinical trials and spontaneous reports (not observed in clinical trials, frequency not known).

The exenatide clinical trials data source comprises 18 placebo controlled trials, 21 active comparator and 2 open-label trials. Background therapies included metformin, a sulfonylurea, a thiazolidinedione, or a combination of oral anti-diabetic agents.

The reactions are listed below as MedDRA preferred term by system organ class and absolute frequency. Patient 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) and not known (cannot be estimated from the available data), including isolated reports.

Table 1: Adverse reactions of BYETTA identified from clinical trials and spontaneous reports

System organ class /adverse reaction	Frequency of occurrence

terms						
	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders						
Anaphylactic reaction				X[1]		
Metabolism and nutrition disorders						
Hypoglycaemia (with metformin and a sulphonylurea) [2]	X[1]					
Hypoglycaemia (with a sulphonylurea)	X[1]					
Decreased appetite		X[1]				
Dehydration, generally associated with nausea, vomiting and/or diarrhoea.			X[1]			
Nervous system disorders						
Headache [2]		X[1]				
Dizziness		X[1]				
Dysgeusia			X[1]			
Somnolence			X[1]			
Gastrointestinal disorders						
Intestinal obstruction				X[1]		
Nausea	X[1]					
Vomiting	X[1]					
Diarrhoea	X[1]					
Dyspepsia		X[1]				
Abdominal pain		X[1]				
Gastroesophageal reflux disease		X[1]				
Abdominal distension		X[1]				
Acute pancreatitis (see section 4.4)						X[3]
Eructation			X[1]			
Constipation		X[1]				
Flatulence		X[1]				
Skin and subcutaneous tissue disorders						
Hyperhidrosis [2]		X[1]				
Alopecia			X[1]			
Macular and papular rash						X[3]
Pruritus, and/ or urticaria		X[1]				
Angioneurotic oedema						X[3]
Renal and urinary disorders						
Altered renal function, including acute renal failure, worsened chronic renal failure, renal impairment, increased serum creatinine			X[1]			
General disorders and administration site conditions						
Feeling jittery		X[1]				
Asthenia [2]		X[1]				
Injection site reactions			X[1]			
Investigations						
Weight decreased			X[1]			
International normalised ratio increased with concomitant warfarin, some reports associated with bleeding						X[3]

[1] Rate based on BYETTA completed long-term efficacy and safety studies n=5763 total (patients on sulphonylurea n=2971).

[2] In insulin-comparator controlled studies in which metformin and a sulphonylurea were concomitant medicinal products, the incidence for these adverse reactions was similar for insulin- and BYETTA-treated patients.

[3] Spontaneous reports data (unknown denominator)

When BYETTA was used in combination with basal insulin therapy the incidence and types of other adverse events observed were similar to those seen in the controlled clinical trials with exenatide as monotherapy, with metformin and/or sulphonylurea or a thiazolidinedione, with or without metformin.

Description of selected adverse reactions

Hypoglycaemia

In studies in patients treated with BYETTA and a sulphonylurea (with or without metformin), the incidence of hypoglycaemia was increased compared to placebo (23.5 % and 25.2 % versus 12.6 % and 3.3 %) and appeared to be dependent on the doses of both BYETTA and the sulphonylurea.

There were no clinically relevant differences in incidence or severity of hypoglycaemia with exenatide compared to placebo, in combination with a thiazolidinedione, with or without metformin. Hypoglycaemia was reported in 11 % and 7 % of patients treated with exenatide and placebo respectively.

Most episodes of hypoglycaemia were mild to moderate in intensity, and resolved with oral administration of carbohydrate.

In a 30-week study, when BYETTA or placebo was added to existing basal insulin therapy(insulin glargine), the dose of basal insulin was decreased by 20 % in patients with an $HbA_{1c} \leq 8.0$ %, per protocol design in order to minimize the risk

of hypoglycaemia. Both treatment arms were titrated to achieve target fasting plasma glucose levels (see section 5.1). There were no clinically significant differences in the incidence of hypoglycaemic episodes in the BYETTA compared to the placebo group (25% and 29% respectively). There were no episodes of major hypoglycaemia in the BYETTA arm.

In a 24-week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin or metformin plus thiazolidinedione the incidence of patients with at least one minor hypoglycaemic episode was 18% and 9% respectively and one patient reported major hypoglycaemia. In patients where existing therapy also included a sulphonylurea the incidence of patients with at least one minor hypoglycaemic episode was 48% and 54% respectively and one patient reported major hypoglycaemia.

Nausea

The most frequently reported adverse reaction was nausea. In patients treated with 5 mcg or 10 mcg BYETTA, 36 % reported at least one episode of nausea. Most episodes of nausea were mild to moderate and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased in most patients who initially experienced nausea.

The incidence of withdrawal due to adverse events was 8 % for BYETTA-treated patients, 3 % for placebo-treated and 1 % for insulin-treated patients in the long-term controlled trials (16 weeks or longer). The most common adverse events leading to withdrawal for BYETTA-treated patients were nausea (4 % of patients) and vomiting (1 %). For placebo-treated or insulin-treated patients, <1 % withdrew due to nausea or vomiting.

BYETTA-treated patients in the open-label extension studies at 82 weeks experienced similar types of adverse events observed in the controlled trials.

Injection site reactions

Injection site reactions have been reported in approximately 5.1 % of subjects receiving BYETTA in long-term (16 weeks or longer) controlled trials. These reactions have usually been mild and usually did not result in discontinuation of BYETTA.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-exenatide antibodies following treatment with BYETTA. In most patients who develop antibodies, antibody titres diminish over time and remain low through 82 weeks.

Overall the percentage of antibody positive patients was consistent across clinical trials. Patients who develop antibodies to exenatide tend to have more injection site reactions (for example: redness of skin and itching), but otherwise similar rates and types of adverse events as those with no anti-exenatide antibodies. In the three placebo-controlled trials (n=963) 38 % of patients had low titre anti-exenatide antibodies at 30 weeks. For this group, the level of glycaemic control (HbA_{1c}) was generally comparable to that observed in those without antibody titres. An additional 6 % of patients had higher titre antibodies at 30 weeks. About half of this 6 % (3 % of the total patients given BYETTA in the controlled studies), had no apparent glycaemic response to BYETTA. In three insulin-comparator controlled trials (n=790) comparable efficacy and adverse events were observed in BYETTA-treated patients regardless of antibody titre.

Examination of antibody-positive specimens from one long-term uncontrolled study revealed no significant cross-reactivity with similar endogenous peptides (glucagon or GLP-1).

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:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

Malta

Byetta 5 micrograms solution for injection, prefilled pen. Byetta ... http://www.medicines.org.uk/emc/print-document?documentId=...

ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Signs and symptoms of overdose may include severe nausea, severe vomiting and rapidly declining blood glucose concentrations. In the event of overdose, appropriate supportive treatment (possibly given parenterally) should be initiated according to the patient's clinical signs and symptoms.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, other blood glucose lowering drugs, excl. insulins, ATC code: A10BX04.

Mechanism of action

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits several antihyperglycaemic actions of glucagon-like peptide-1 (GLP-1). The amino acid sequence of exenatide partially overlaps that of human GLP-1. Exenatide has been shown to bind to and activate the known human GLP-1 receptor *in vitro*, its mechanism of action mediated by cyclic AMP and/or other intracellular signaling pathways.

Exenatide increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells. As blood glucose concentrations decrease, insulin secretion subsides. When exenatide was used in combination with metformin alone, no increase in the incidence of hypoglycaemia was observed over that of placebo in combination with metformin which may be due to this glucose-dependent insulinotropic mechanism. (see section 4.4).

Exenatide suppresses glucagon secretion which is known to be inappropriately elevated in type 2 diabetes. Lower glucagon concentrations lead to decreased hepatic glucose output. However, exenatide does not impair the normal glucagon response and other hormone responses to hypoglycaemia.

Exenatide slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation.

Pharmacodynamic effects

BYETTA improves glycaemic control through the immediate and sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

Clinical efficacy and safety

Studies of BYETTA with metformin, a sulphonylurea or both as background therapy

The clinical studies comprised 3945 subjects (2997 treated with exenatide), 56 % men and 44 % women, 319 subjects (230 treated with exenatide) were ≥70 years of age and 34 subjects (27 treated with exenatide) were ≥75 years of age.

BYETTA reduced HbA_{1c} and body weight in patients treated for 30 weeks in three placebo-controlled studies, whether the BYETTA was added to metformin, a sulphonylurea or a combination of both. These reductions in HbA_{1c} were generally observed at 12 weeks after initiation of treatment. See Table 2. The reduction in HbA_{1c} was sustained and the weight loss continued for at least 82 weeks in the subset of 10 mcg BID patients completing both the placebo-controlled studies and the uncontrolled study extensions (n=137).

Table 2: Combined results of the 30 week placebo controlled studies (intent to treat patients)

	Placebo	BYETTA 5 mcg BID	BYETTA 10 mcg BID
N	483	480	483
Baseline HbA_{1c}(%)	8.48	8.42	8.45
HbA_{1c}(%) change from base line	0.08	-0.59	-0.89
Proportion of patients (%) achieving HbA_{1c} ≤7%	7.9	25.3	33.6
Proportion of patients (%) achieving HbA_{1c} ≤7% (patients completing studies)	10.0	29.6	38.5
Baseline weight(kg)	99.26	97.10	98.11

Change of weight from baseline (kg)	-0.65	-1.41	-1.91

In insulin-comparator studies BYETTA (5 mcg BID for 4 weeks, followed by 10 mcg BID) in combination with metformin and sulphonylurea significantly (statistically and clinically) improved glycaemic control, as measured by decrease in HbA_{1c}. This treatment effect was comparable to that of insulin glargine in a 26-week study (mean insulin dose 24.9 IU/day, range 4-95 IU/day, at the end of study) and biphasic insulin aspart in a 52-week study (mean insulin dose 24.4 IU/day, range 3-78 IU/day, at the end of study). BYETTA lowered HbA_{1c} from 8.21 (n=228) and 8.6 % (n=222) by 1.13 and 1.01 % while insulin glargine lowered from 8.24 (n=227) by 1.10 % and biphasic insulin aspart from 8.67 (n=224) by 0.86 %. Weight loss of 2.3 kg (2.6 %) was achieved with BYETTA in the 26 week study and a loss of 2.5 kg (2.7 %) in a 52-week study whereas treatment with insulin was associated with weight gain. Treatment differences (BYETTA minus comparator) were -4.1 kg in the 26-week study and –5.4 kg in the 52-week study. Seven-point self-monitored blood glucose profiles (before and after meals and at 3 am) demonstrated significantly reduced glucose values compared to insulin in the postprandial periods after BYETTA injection. Premeal blood glucose concentrations were generally lower in patients taking insulin compared to BYETTA. Mean daily blood glucose values were similar between BYETTA and insulin. In these studies the incidence of hypoglycaemia was similar for BYETTA and insulin treatment.

Studies of BYETTA with metformin, a thiazolidinedione or both as background therapy

Two placebo-controlled studies were conducted: one of 16 and one of 26 weeks duration, with 121 and 111 BYETTA and 112 and 54 placebo treated patients respectively, added to existing thiazolidinedione treatment, with or without metformin. Of the BYETTA patients, 12% were treated with a thiazolidinedione and BYETTA and 82% were treated with a thiazolidinedione, metformin and BYETTA. BYETTA (5 mcg BID for 4 weeks, followed by 10 mcg BID) resulted in statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.7% versus +0.1%) as well as significant reductions in body weight (-1.5 versus 0 kg) in the 16 week study. The 26 week study showed similar results with statistically significant reductions from baseline HbA_{1c} compared to placebo (-0.8% versus -0.1%). There was no significant difference in body weight between treatment groups in change from baseline to endpoint (-1.4 versus -0.8 kg).

When BYETTA was used in combination with a thiazolidinedione, the incidence of hypoglycaemia was similar to that of placebo in combination with a thiazolidinedione. The experience in patients > 65 years and in patients with impaired renal function is limited. The incidence and type of other adverse events observed were similar to those seen in the 30-week controlled clinical trials with a sulphonylurea, metformin or both.

Studies of BYETTA in combination with basal insulin

In a 30-week study, either BYETTA (5 mcg BID for 4 weeks, followed by 10 mcg BID) or a placebo was added to insulin glargine (with or without metformin, pioglitazone or both). During the study both treatment arms titrated insulin glargine using an algorithm reflecting current clinical practice to a target fasting plasma glucose of approximately 5.6 mmol/l. The mean age of subjects was 59 years and the mean duration of diabetes was 12.3 years.

At the end of the study, BYETTA (n=137) demonstrated a statistically significant reduction in the HbA_{1c} and weight compared to placebo (n=122). BYETTA lowered HbA_{1c} by 1.7 % from a baseline of 8.3 % while placebo lowered HbA_{1c} by 1.0 % from a baseline of 8.5 %. The proportion of patients achieving HbA_{1c} <7% and HbA_{1c} ≤6.5% was 56 % and 42 % with BYETTA and 29 % and 13 % with placebo. Weight loss of 1.8 kg from a baseline of 95 kg was observed with BYETTA whereas a weight gain of 1.0 kg from a baseline of 94kg was observed with placebo.

In the BYETTA arm the insulin dose increased by 13 units/day compared to 20 units/ day on the placebo arm. BYETTA reduced fasting serum glucose by 1.3 mmol/l and placebo by 0.9 mmol/l. BYETTA arm compared to placebo had significantly lowered postprandial blood glucose excursions at the morning meal (- 2.0 versus - 0.2 mmol/l) and evening meal (- 1.6 versus + 0.1 mmol/l), there was no difference between treatments at midday.

In a 24-week study, where either insulin lispro protamine suspension or insulin glargine was added to existing therapy of BYETTA and metformin, metformin and sulphonylurea or metformin and pioglitazone, HbA1c was lowered by 1.2 % (n=170) and by 1.4 % (n=167) respectively from a baseline of 8.2 %. Weight increase of 0.2 kg was observed for patients on insulin lispro protamine suspension and 0.6 kg for insulin glargine treated patients from a baseline of 102 kg and 103 kg respectively.

In a 30-week, open-label, active comparator-controlled, noninferiority study, the safety and efficacy of BYETTA (n=315) versus titrated insulin lispro three times daily (n=312) on a background of optimized basal insulin glargine and metformin in patients with type 2 diabetes was evaluated.

Following a basal insulin optimization (BIO) phase, patients with HbA_{1c} >7.0% were randomized to add either BYETTA or insulin lispro to their existing regimen of insulin glargine and metformin. In both treatment groups, subjects continued to titrate their insulin glargine doses using an algorithm reflecting current clinical practice.

All patients assigned to BYETTA initially received 5 mcg BID for four weeks. After four weeks, their dose was increased to 10 mcg BID. Patients in the BYETTA-treated group with an HbA_{1c}≤8.0% at the end of the BIO phase decreased their insulin glargine dose by at least 10%.

BYETTA lowered HbA_{1c} by 1.1% from a baseline of 8.3% and insulin lispro lowered HbA_{1c} by 1.1% from a baseline of 8.2% and noninferiority of BYETTA to titrated lispro was demonstrated. The proportion of patients achieving HbA_{1c} <7% was 47.9% with BYETTA and 42.8% with insulin lispro. Weight loss of 2.6 kg from a baseline of 89.9 kg was observed with BYETTA whereas a weight gain of 1.9 kg from a baseline of 89.3 kg was observed with insulin lispro.

Byetta 5 micrograms solution for injection, prefilled pen. Byetta ... http://www.medicines.org.uk/emc/print-document?documentId=...

Fasting lipids

BYETTA has shown no adverse effects on lipid parameters. A trend for a decrease in triglycerides has been observed with weight loss.

Beta-cell function

Clinical studies with BYETTA have indicated improved beta-cell function, using measures such as the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio.

A pharmacodynamic study demonstrated in patients with type 2 diabetes (n=13) a restoration of first phase insulin secretion and improved second phase insulin secretion in response to an intravenous bolus of glucose.

Body weight

A reduction in body weight was seen in patients treated with BYETTA irrespective of the occurrence of nausea although the reduction was larger in the group with nausea (mean reduction 2.4 kg versus 1.7 kg) in the long term controlled studies of up to 52 weeks.

Administration of exenatide has been shown to reduce food intake, due to decreased appetite and increased satiety.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with BYETTA in one or more subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration to patients with type 2 diabetes, exenatide reaches median peak plasma concentrations in 2 h. Mean peak exenatide concentration (C_{max}) was 211 pg/ml and overall mean area under the curve (AUC_{0-inf}) was 1036 pg •h/ml following subcutaneous administration of a 10 mcg dose of exenatide. Exenatide exposure increased proportionally over the therapeutic dose range of 5 mcg to 10 mcg. Similar exposure is achieved with subcutaneous administration of exenatide in the abdomen, thigh, or arm.

Distribution

The mean apparent volume of distribution of exenatide following subcutaneous administration of a single dose of exenatide is 28 l.

Biotransformation and elimination

Nonclinical studies have shown that exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. In clinical studies the mean apparent clearance of exenatide is 9 l/h and the mean terminal half-life is 2.4 h. These pharmacokinetic characteristics of exenatide are independent of the dose.

Special populations

Renal impairment

In patients with mild (creatinine clearance 50 to 80 ml/min) or moderate renal impairment (creatinine clearance 30 to 50 ml/min), exenatide clearance was mildly reduced compared to clearance in individuals with normal renal function (13 % reduction in mild and 36 % reduction in moderate renal impairment). Clearance was significantly reduced by 84 % in patients with end-stage renal disease receiving dialysis (see section 4.2).

Hepatic insufficiency

No pharmacokinetic study has been performed in patients with hepatic insufficiency. Exenatide is cleared primarily by the kidney, therefore hepatic dysfunction is not expected to affect blood concentrations of exenatide.

Gender and race

Gender and race have no clinically relevant influence on exenatide pharmacokinetics.

Elderly

Long-term controlled data in elderly are limited, but suggest no marked changes in exenatide exposure with increased age up to about 75 years old. In a pharmacokinetic study in patients with type 2 diabetes, administration of exenatide (10 mcg) resulted in a mean increase of exenatide AUC by 36 % in 15 elderly subjects aged 75 to 85 years compared to 15 subjects aged 45 to 65 years likely related to reduced renal function in the older age group (see section 4.2).

Paediatric population

In a single-dose pharmacokinetic study in 13 patients with type 2 diabetes and between the ages of 12 and 16 years,

administration of exenatide (5 mcg) resulted in slightly lower mean AUC (16% lower) and C_{max} (25% lower) compared to those observed in adults.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, or genotoxicity.

In female rats given exenatide for 2 years, an increased incidence of benign thyroid C−cell adenomas was observed at the highest dose, 250 mcg/kg/day, a dose that produced an exenatide plasma exposure 130-fold the human clinical exposure. This incidence was not statistically significant when adjusted for survival. There was no tumorigenic response in male rats or either sex of mice.

Animal studies did not indicate direct harmful effects with respect to fertility or pregnancy. High doses of exenatide during mid-gestation caused skeletal effects and reduced foetal growth in mice and reduced foetal growth in rabbits. Neonatal growth was reduced in mice exposed to high doses during late gestation and lactation.

6. Pharmaceutical particulars

6.1 List of excipients

metacresol

mannitol

glacial acetic acid

sodium acetate trihydrate

water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

Shelf life for pen in use: 30 days.

6.4 Special precautions for storage

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.

In use

Store below 25 °C.

The pen should not be stored with the needle attached.

Replace cap on pen in order to protect from light.

6.5 Nature and contents of container

Type I glass cartridge with a (bromobutyl) rubber plunger, rubber disc, and aluminium seal. Each cartridge is assembled into a disposable pen-injector (pen).

Each Byetta 5 mcg pre-filled pen contains 60 doses of sterile preserved solution (approximately 1.2 ml)

Each Byetta 10 mcg pre-filled pen contains 60 doses of sterile preserved solution (approximately 2.4ml)

Pack size of 1 and 3 pens. Not all pack sizes may be marketed.

Injection needles are not included.

Becton, Dickinson and Company needles are suitable to use with the BYETTA pen.

6.6 Special precautions for disposal and other handling

The patient should be instructed to discard the needle after each injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Byetta 5 micrograms solution for injection, prefilled pen. Byetta ... http://www.medicines.org.uk/emc/print-document?documentId=...

Instructions for use

BYETTA is for use by one person only.

The instructions for using the pen, included with the leaflet, must be followed carefully.

The pen is stored without needle.

BYETTA should not be used if particles appear or if the solution is cloudy and/or coloured.

BYETTA that has been frozen must not be used.

7. Marketing authorisation holder

AstraZeneca AB

SE-151 85 Södertälje

Sweden

8. Marketing authorisation number(s)

EU/1/06/362/001: 5 µg (1 pen)

EU/1/06/362/002: 5 µg (3 pens)

EU/1/06/362/003: 10 µg (1 pen)

EU/1/06/362/004: 10 µg (3 pens)

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 20 November 2006

Date of latest renewal: 20 November 2011

10. Date of revision of the text

16th December 2015

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

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For use with question 10 & 11, please turn over:

Fentalis Reservoir 25 microgram/hour Transdermal Patches

Summary of Product Characteristics Updated 09-Jun-2015 | Sandoz Limited

1. Name of the medicinal product

Fentalis Reservoir 25 microgram/hour transdermal patches

2. Qualitative and quantitative composition

Each transdermal patch (active surface area 10 cm^2) contains 2.5 mg fentanyl (corresponding to 25 microgram/hour fentanyl release rate).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Transdermal patch

Transparent and oblong transdermal patch which consists of a protective layer (to be removed prior to application of the patch) and four functional layers: an occlusive backing, a drug reservoir, a release membrane and an adhesive surface.

Surface area of the transdermal patch:

Fentalis Reservoir 25 microgram/hour transdermal patches: 10 cm^2

4. Clinical particulars

4.1 Therapeutic indications

Adults:

Chronic severe pain requiring treatment with opioid analgesics, e.g. cancer pain.

Children:

Long term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

4.2 Posology and method of administration

Fentalis Reservoir transdermal patches release fentanyl over 72 hours. The fentanyl release rate is 25 microgram/hour and the corresponding active surface area is 10 cm^2.

The required fentanyl dosage is adjusted individually and should be assessed regularly after each administration.

Posology

Adults:

Initial dose selection:

The appropriate initiating dose of Fentalis Reservoir transdermal patches should be based on the patient's current opioid use. Other factors to be considered are the current general condition and medical status of the patient, including body size, age, and extent of debilitation as well as degree of opioid tolerance.

Patients receiving opioid treatment for the first time

In opioid-naïve patients, who have not previously been treated with opioids, the initial dosage should not exceed 25 microgram/hour.

Clinical experience with Fentalis Reservoir transdermal patches is limited in opioid-naïve patients. In the circumstances in which therapy with Fentalis Reservoir transdermal patches is considered appropriate in opioid-naïve patients, it is recommended that these patients be titrated with low doses of immediate release opioids (e.g., morphine) to attain equianalgesic dosage relative to Fentalis Reservoir transdermal patches with a release rate of 25 micrograms/hour. Patients can then be converted to Fentalis Reservoir transdermal patches 25 microgram/hour. The dose may subsequently be titrated upwards, if required, to achieve the lowest appropriate dose of Fentalis Reservoir transdermal patches depending on the response and supplementary analgesic requirements.

In opioid-naïve older or weak patients, it is not recommended to initiate an opioid treatment with Fentalis Reservoir transdermal patches, due to their known susceptibility to opioid treatments. In these cases, it would be preferable to initiate a treatment with low doses of immediate release morphine and to prescribe Fentalis Reservoir transdermal patches after determination of the optimal dosage.

Changing from other opioid treatment

When changing over from oral or parenteral opioids to fentanyl treatment, the initial dosage should be calculated as follows:

1. The quantity of analgesics required over the last 24 hours should be determined.

2. The obtained sum should be converted to the corresponding oral morphine dosage using Table 1.

3. The corresponding fentanyl dosage should be determined as follows.

a) using Table 2 for patients who have a need for opioid rotation (conversion ratio of oral morphine to transdermal fentanyl equal to 150:1)

b) using Table 3 for patients on stable and well tolerated opioid therapy (conversion ratio of oral morphine to transdermal fentanyl equal to 100:1).

Table 1: Equianalgesic potency conversion

All i.m. and oral dosages given in the table are equivalent in analgesic effect to 10 mg morphine administered intramuscularly.

Active substance	**Equianalgesic doses (mg)**	
	i.m.*	**Oral**
Morphine	10	30–40 (assuming repeated dosing)
Hydromorphone	1.5	7.5
Methadone	10	20
Oxycodone	15	30
Levorphanol	2	4
Oxymorphone	1	10 (rectal)
Diamorphine	5	60
Pethidine	75	-
Codeine	130	200
Buprenorphine	0.4	0.8 (sublingual)
Ketobemidone	10	20–30

* Based on single-dose studies in which the i.m. dose of each above-mentioned agent was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.

Table 2: Recommended initial dosage of Fentalis Reservoir transdermal patches based upon the oral daily morphine dosage (for patients who have a need for opioid rotation)

Oral morphine (mg/24 h)	**Dosage of Fentalis Reservoir transdermal patches (microgram/hour)**
90-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

Table 3: Recommended initial dosage of Fentalis Reservoir transdermal patches based upon the oral daily morphine dosage (for patients on stable and well tolerated opioid therapy)

Oral	**Dosage of Fentalis Reservoir**

morphine (mg/24 h)	**transdermal patches (microgram/hour)**
60-89	25
90-149	50
150-209	75
210-269	100
270-329	125
330-389	150
390-449	175
450-509	200
510-569	225
570-629	250
630-689	275
690-749	300

The oral morphine dosages in Table 2 and 3 were used as a basis in clinical trials when changing medication to Fentalis Reservoir transdermal patches. Other conversion schemes which have proved their usefulness in clinical practice exist and may be applied.

Previous analgesic therapy should be phased out gradually from the time of the first patch application until analgesic efficacy with Fentalis Reservoir transdermal patches is attained. For both strong opioid-naïve and opioid tolerant patients, the initial evaluation of the analgesic effect of Fentalis Reservoir transdermal patches should not be made until the patch has been worn for 24 hours due to the gradual increase in serum fentanyl concentrations up to this time.

Dose titration and maintenance therapy

The Fentalis Reservoir transdermal patches should be replaced every 72 hours. The dose should be titrated individually until the analgesic efficacy is attained. In patients who experience a marked decrease in analgesia in the period of 48-72 hours after application, replacement of the Fentalis Reservoir transdermal patches after 48 hours may be necessary. If analgesia is insufficient at the end of the initial application period, the dose may be increased at intervals of 3 days, until the desired effect is obtained for each patient. The dosage is normally raised in increments of 25 microgram/hour (oral morphine 90 mg/day ≈ Fentalis Reservoir transdermal patches 25 micrograms/h), but the need for additional medication and the pain experienced by the patient should be taken into account. When the required dosage exceeds 100 microgram/hour, more than one Fentalis Reservoir transdermal patches may be used to achieve the desired dose. Patients may require periodic supplemental doses of a short-acting analgesic for "breakthrough" pain. Additional or alternative methods of analgesia should be considered when the transdermal fentanyl dose exceeds 300 microgram/hour.

Conversion or discontinuation of treatment

If discontinuation of Fentalis Reservoir transdermal patches is necessary, any replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl serum concentrations fall gradually after Fentalis Reservoir transdermal patches is removed, it takes 17 hours or more for the fentanyl serum concentrations to decrease 50% (see section 5.2). As a general rule, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms.

Opioid withdrawal symptoms (see section 4.8) are possible in some patients after conversion or dose adjustment.

Tables 2 and 3 should not be used to convert from Fentalis Reservoir transdermal patches to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Use in older patients

Older patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see sections 4.4 and 5.2).

Paediatric population:

Children aged *16 years and above:*

follow adult dosage

Children aged 2 to 16 years old:

Fentalis Reservoir transdermal patches should be administered **only to opioid-tolerant paediatric patients (ages 2 to 16 years)** who are already receiving at least 45 mg oral morphine equivalents per day. A lower starting dose and the titration schedule in children may require a fentanyl release rate of less than 25 microgram/hour. In the case of Fentalis Reservoir transdermal patches, due to the dose strengths of this product starting at 25 microgram/hour, use in children is not recommended and use of other Fentalis Reservoir transdermal patches should be considered.

To convert paediatric patients from oral opioids to Fentalis Reservoir transdermal patches refer to Table 4.

Table 4: Recommended Fentalis Reservoir transdermal patch dose based upon daily oral morphine dose[1]

Oral 24 hour morphine (mg/day)	**Fentalis Reservoir transdermal patch (microgram/hour)**
For paediatric patients[2]	
30 – 44	12.5
45 – 134	25

[1] In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to Fentalis Reservoir transdermal patches

[2] Conversion to Fentalis Reservoir transdermal patches doses greater than 25 micrograms/h is the same for adult and paediatric patients

For children who receive more than 90 mg oral morphine a day, only limited information is currently available from clinical trials. In the paediatric studies, the required Fentalis Reservoir transdermal patch dose was calculated conservatively: 30 mg to 44 mg oral morphine per day or its equivalent opioid dose was replaced by one Fentalis Reservoir transdermal patch 12.5 microgram/hour. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to Fentalis Reservoir transdermal patches. The conversion schedule should not be used to convert from Fentalis Reservoir transdermal patches into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of Fentalis Reservoir transdermal patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Fentalis Reservoir transdermal patches, the patient should be given the previous regular dose of analgesics. In the next 12 hours, these analgesics should be provided based on clinical need.

Since peak fentanyl levels occur after 12 to 24 hours of treatment, monitoring of the paediatric patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of Fentalis Reservoir transdermal patches therapy or up-titration of the dose (see also section 4.4).

Dose titration and maintenance

If the analgesic effect of Fentalis Reservoir transdermal patches is insufficient, supplementary morphine or another short-duration opioid should be administered. Depending on the additional analgesic needs and the pain status of the child, it may be decided to increase the dose of transdermal fentanyl. Dose adjustments should be done in 12.5 microgram/hour steps. Due to the dosage strengths of this product starting at 25 microgram/hour, other Fentalis Reservoir transdermal patches with lower dosages should be used.

Use in patients with hepatic or renal impairment

Patients with impaired hepatic or renal function should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4).

Use in febrile patients

Dose adjustment may be necessary in patients during episodes of fever (see section 4.4).

Method of administration

For transdermal use.

Fentalis Reservoir transdermal patches should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arm. In young children, the upper back is the preferred location to apply the patch, to minimise the potential of the child removing the patch. A non-hairy area should be selected. If this is not possible, hair at the application site should be clipped (not shaved) prior to system application. If the site of application requires to be cleansed prior to application of the patch, this should be done with water. Soaps, oils, lotions, alcohol or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before application of the patch.

Since the transdermal patch is protected outwardly by a waterproof covering foil, it may also be worn when taking a shower.

Fentalis Reservoir transdermal patch is to be attached as soon as the pack has been opened. Following removal of the protective layer, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. An additional fixing of the transdermal patch

may be necessary.

Duration of administration

The patch should be changed after 72 hours. If an earlier change becomes necessary in individual cases, no change should be made before 48 hours have elapsed, otherwise a rise in mean fentanyl concentrations may occur. A new skin area must be selected for each application. A period of 7 days should be allowed to elapse before applying a new patch to the same area of skin. The analgesic effect may persist for some time after removal of the transdermal patch.

If traces of the transdermal patch remain on the skin after removal of the patch, these can be cleaned off using copious amounts of soap and water. No alcohol or other solvents must be used for cleaning as these may penetrate the skin due to the effect of the patch.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- Acute or postoperative pain, since dosage titration is not possible during short-term use and because serious and life-threatening hypoventilation could result

- Severly impaired central nervous system function

- Severe respiratory depression

4.4 Special warnings and precautions for use

PATIENTS WHO HAVE EXPERIENCED SERIOUS ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 24 HOURS AFTER FENTALIS RESERVOIR TRANSDERMAL PATCHES REMOVAL OR MORE AS CLINICAL SYMPTOMS DICTATE BECAUSE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND ARE REDUCED BY ABOUT 50% 17 (RANGE 13-22) HOURS LATER.

Fentalis Reservoir transdermal patches should be kept out of reach of children at all times before and after use.

Fentalis Reservoir transdermal patches should not be divided, cut or damaged in any other way, since this would result in the uncontrolled release of fentanyl. A patch that has been divided, cut or damaged in any way should not be used.

It is not possible to ensure the interchangeability of different makes of fentanyl transdermal patches in individual patients. Therefore, it should be emphasised that patients should not be changed from one make of fentanyl transdermal patches to another without specific counselling on the change from their healthcare professionals.

Breakthrough pain

Studies have shown that almost all patients, despite treatment with a fentanyl transdermal patch, require supplemental treatment with potent rapid-release medicinal products to arrest breakthrough-pain.

Respiratory depression

As with all potent opioids, some patients may experience significant respiratory depression with Fentalis Reservoir transdermal patches; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the transdermal patch. The incidence of respiratory depression increases as the fentanyl dose is increased (see also section 4.9). CNS active substancess may increase the respiratory depression (see section 4.5).

Opioid-naïve and not opioid-tolerant states

Use of fentanyl transdermal patch in opioid-naïve patients has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of fentanyl transdermal system is used in initiating therapy in opioid-naïve patients. It is recommended that fentanyl transdermal patch be used in patients who have demonstrated opioid tolerance (see section 4.2).

Chronic pulmonary disease

Fentanyl may have more severe adverse effects in patients with chronic obstructive or other pulmonary disease. In such patients, opioids may decrease respiratory drive and increase airway resistance.

Drug dependence and potential for abuse

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is rare. Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of Fentalis Reservoir transdermal patch may result in overdose and/or death.

Patients with a prior history of drug dependence/alcohol abuse are more at risk to develop dependence and abuse in opioid treatment. Patients at increased risk of opioid abuse may still be appropriately treated with modified-release opioid formulations; however, these patients will require monitoring for signs of misuse, abuse, or addiction.

Increased intracranial pressure

Fentalis Reservoir 25 microgram/hour Transdermal Patches - (... http://www.medicines.org.uk/emc/print-document?documentId=...

Fentalis Reservoir transdermal patches should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Fentalis Reservoir transdermal patch should be used with caution in patients with brain tumours.

Cardiac diseases

Fentanyl may cause bradycardia and should therefore be administered with caution to patients with bradyarrhythmias.

Opioids may cause hypotension, especially in patients with acute hypovolaemia. Underlying, symptomatic hypotension and/or hypovolaemia should be corrected before treatment with Fentalis Reservoir transdermal patches is initiated.

Hepatic impairment

Because fentanyl is metabolised to pharmacologically inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive Fentalis Reservoir transdermal patches, they should be observed carefully for signs of fentanyl toxicity and the dose of Fentalis Reservoir transdermal patches reduced if necessary (see section 5.2).

Renal impairment

Less than 10% of fentanyl is excreted unchanged by the kidney and, unlike morphine, there are no known active metabolites eliminated by the kidneys. If patients with renal impairment receive Fentalis Reservoir transdermal patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2).

Fever/external heat application

A pharmacokinetic model suggests that serum fentanyl concentrations may increase by about one-third if the skin temperature increases to 40 °C. Therefore, patients with fever should be monitored for opioid side effects and the Fentalis Reservoir transdermal patch dose should be adjusted if necessary. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death. A clinical pharmacology trial conducted in healthy adult subjects has shown that the application of heat over the Fentalis Reservoir transdermal patch system increased mean fentanyl AUC values by 120% and mean C_{max} values by 61%.

All patients should be advised to avoid exposing the Fentalis Reservoir transdermal patch application site to direct external heat sources such as heating pads, hot water bottles, electric blankets, heated water beds, heat or tanning lamps, intensive sunbathing, prolonged hot baths, saunas and hot whirlpool spa baths.

Serotonin syndrome

Caution is advised when Fentalis Reservoir transdermal patches are coadministered with medicinal products that affect the serotonergic neurotransmitter systems. The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic active substances such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with active substances which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyper-reflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g, nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, rapid discontinuation of Fentalis Reservoir transdermal patches should be considered.

Interactions with CYP3A4 inhibitors

The concomitant use of transdermal fentanyl with cytochrome P450 (CYP)3A4 inhibitors (e.g. ritonavir, ketoconazole, itraconazole, fluconazole, voriconazole, troleandomycin, clarithromycin, erythromycin, nelfinavir, nefazodone, verapamil, diltiazem and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation special patient care and observation are appropriate. Therefore, the concomitant use of transdermal fentanyl and CYP3A4 inhibitors is not recommended unless the patient is closely monitored. Patients, especially those who are receiving fentanyl transdermal patches and CYP3A4 inhibitors, should be monitored for signs of respiratory depression and dosage adjustments should be made if warranted.

Accidental exposure by patch transfer

Accidental transfer of a fentanyl transdermal patch to the skin of a non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer (see section 4.9).

Use in older patients

Data from intravenous studies with fentanyl suggest that older patients may have reduced clearance, a prolonged

half-life and they may be more sensitive to the active substance than younger patients. If older patients receive Fentalis Reservoir transdermal patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2).

Paediatric population

Fentalis Reservoir transdermal patch should not be administered to **opioid naïve paediatric patients** (see section 4.2). The potential for serious or life-threatening hypoventilation exists regardless of the dose of transdermal fentanyl administered.

Transdermal fentanyl has not been studied in children under 2 years of age. Fentalis Reservoir transdermal patches should be administered only to opioid-tolerant children aged 2 years or older (see section 4.2). Fentalis Reservoir transdermal patches should not be used in children under 2 years of age.

To guard against accidental ingestion by children, use caution when choosing the application site for Fentalis Reservoir transdermal patches (see sections 4.2 and 6.6) and monitor adhesion of the patch closely**.**

Gastrointestinal tract

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with Fentalis Reservoir transdermal patches should be stopped.

Patients with myasthenia gravis

Non-epileptic (myo)clonic reactions can occur. Caution should be exercised when treating patients with myasthenia gravis.

Athletes must be aware that this medicine may cause a positive reaction to 'anti-doping' tests.

For disposal instructions see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Other central nervous system depressants

Fentanyl may produce additive depressant effects with other central nervous system depressants, including:

• opioids

• sedatives

• hypnotics

• general anaesthetics

• phenothiazines

• anxiolytics and tranquillizer

• antipsychotics

• skeletal muscle relaxants

• sedating antihistamines

• alcoholic beverages

Concomitant use may result in hypoventilation, hypotension, profound sedation, coma or death. Therefore, the use of any of the above mentioned concomitant medicinal products requires special patient care and observation. Dose reduction of one or both medicinal products should be taken into consideration.

CYP3A4 inhibitors

Fentanyl, a high clearance active substance, is rapidly and extensively metabolised mainly by CYP3A4.

The concomitant use of transdermal fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. ritonavir, ketoconazole, itraconazole, fluconazole, voriconazole, troleandomycin, clarithromycin, erythromycin, nelfinavir, nefazodone, verapamil, diltiazem, and amiodarone) may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored. (see section 4.4)

CYP3A4 inducers

The concomitant use with CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin) could result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. This may require a dose adjustment of transdermal fentanyl. After stopping the treatment of a CYP3A4 inducer, the effects of the inducer decline gradually and

Fentalis Reservoir 25 microgram/hour Transdermal Patches - (... http://www.medicines.org.uk/emc/print-document?documentId=...

may result in a fentanyl plasma increase concentration which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. In this situation, careful monitoring and dose adjustment should be made if warranted.

Monoamine Oxidase Inhibitors (MAOI)

Fentalis Reservoir transdermal patch is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotoninergic effects, have been reported. Therefore, Fentalis Reservoir transdermal patches should not be used within 14 days after discontinuation of treatment with MAOIs.

Serotonergic medicinal products

Coadministration of transdermal fentanyl with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

Concomitant use of mixed agonists/antagonists

The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Fentalis Reservoir transdermal patch in pregnant women. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Fentanyl crosses the placenta. Neonatal withdrawal syndrome has been reported in newborn infants with chronic maternal use of Fentalis Reservoir transdermal patch during pregnancy. Fentalis Reservoir transdermal patches should not be used during pregnancy unless clearly necessary.

Use of Fentalis Reservoir transdermal patch during childbirth is not recommended because it should not be used in the management of acute or postoperative pain (see section 4.3). Moreover, because fentanyl passes through the placenta, the use of Fentalis Reservoir transdermal patches during childbirth might result in respiratory depression in the newborn infant.

Breast-feeding

Fentanyl is excreted into breast milk and may cause sedation and respiratory depression in the breastfed infant. Breast-feeding should therefore be discontinued during treatment with Fentalis Reservoir transdermal patches and for at least 72 hours after removal of the patch.

4.7 Effects on ability to drive and use machines

Fentalis Reservoir transdermal patches may impair the mental and/or physical ability required to perform potentially hazardous tasks such as driving a car or operating machinery. Patients stabilized on a specific dosage - without further interference from other medicinal products - will not necessarily be restricted. Caution is required especially at the beginning of treatment, at dosage increases as well as in connection with other medicinal products since the ability to drive and use machines may be impaired.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called 'statutory defence') if:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely.

4.8 Undesirable effects

The safety of Fentalis Reservoir transdermal patches was evaluated in 1854 adult and paediatric subjects who participated in 11 clinical trials (double-blind fentanyl patch [placebo or active control] and/or open label fentanyl patch [no control or active control]) used for the management of chronic malignant or non-malignant pain. These subjects took

at least 1 dose of Fentalis Reservoir transdermal patch and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported adverse drug reactions (ADRs) were (with % incidence): nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), and headache (11.8%).

The most serious undesirable effect of fentanyl is respiratory depression.

The ADRs reported with the use of Fentalis Reservoir transdermal patches from these clinical trials, including the above-mentioned ADRs, and from post-marketing experiences are listed below.

The displayed frequency categories use the following convention: 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); and not known (cannot be estimated from the available data).

System organ class	Adverse drug reactions				
	Frequency category				
	Very Common	Common	Uncommon	Rare	Not known
Immune system disorders		Hypersensitivity			Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Metabolism and nutrition disorders		Anorexia			
Psychiatric disorders		Insomnia, Depression, Anxiety, Confusional state, Hallucination	Agitation, Disorientation, Euphoric mood		
Nervous system disorders	Somnolence, Dizziness, Headache[1]	Tremor, Paraesthesia	Hypoaesthesia, Convulsion (including clonic convulsions and grand mal convulsion), Amnesia Depressed level of consciousness, Loss of consciousness		
Eye disorders			Blurred vision	Miosis	
Ear and labyrinth disorders		Vertigo			
Cardiac disorders		Palpitations, Tachycardia	Bradycardia, Cyanosis	Arrythmia	
Vascular disorders		Hypertension	Hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Respiratory depression, Respiratory distress	Apnoea, Hypoventilation	Bradypnoea
Gastrointestinal disorders	Nausea[1], Vomiting[1], Constipation[1]	Diarrhoea[1], Dry mouth, Abdominal pain, Upper abdominal pain, Dyspepsia	Ileus	Subileus	
Skin and subcutaneous tissue disorders		Hyperhidrosis, Pruritus[1], Rash, Erythema	Eczema, Allergic dermatitis, Skin disorder, Dermatitis, Contact dermatitis		
Musculoskeletal and connective tissue disorders		Muscle spasms	Muscle twitching		
Renal and urinary disorders		Urinary retention			
Reproductive system and breast disorders			Erectile dysfunction, Sexual dysfunction		
General disorders and administration site conditions		Fatigue, Peripheral oedema Asthenia, Malaise, Feeling cold	Application site reaction, Influenza like illness, Feeling of body temperature change, Application site hypersensitivity, Drug withdrawal syndrome[2], Pyrexia	Application site dermatitis, Application site eczema	

[1] see “paediatric subjects” below

[2] see “description of selected adverse reactions” below

Description of selected adverse reactions

As with other opioid analgesics, tolerance, physical dependence, and psychological dependence can develop on repeated use of Fentalis Reservoir transdermal patches (see section 4.4).

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety, and shivering) are possible in some patients after conversion from their previous opioid analgesic to Fentalis Reservoir transdermal patch or if therapy is stopped suddenly (see section 4.2).

There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used Fentalis Reservoir transdermal patches during pregnancy (see section 4.6).

Paediatric population

The adverse event profile in children and adolescents treated with Fentalis Reservoirtransdermal patch was similar to that observed in adults. No risk was identified in the paediatric population beyond that expected with the use of opioids for the relief of pain associated with serious illness and there does not appear to be any paediatric-specific risk associated with Fentalis Reservoir transdermal patch use in children as young as 2 years old when used as directed. Very common adverse events reported in paediatric clinical trials were fever, headache, vomiting, nausea, constipation, diarrhoea and pruritus.

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 (www.mhra.gov.uk/yellowcard).

4.9 Overdose

Symptoms

The manifestations of fentanyl overdose are an extension of its pharmacological actions, the most serious effect being respiratory depression.

Treatment

For management of respiratory depression, immediate countermeasures include removing the Fentalis Reservoir transdermal patches and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone.

Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotisation after the patch is removed; repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube, and oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, hypovolaemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, opioids, phenylpiperidine derivatives

ATC code: N02AB03

Fentanyl is an opioid analgesic which interacts predominantly with the μ-opioid receptor. Its principal therapeutic effects are analgesia and sedation. The serum concentrations of fentanyl that cause a minimal analgesic effect in opioid-naïve patients fluctuate between 0.3-1.5 ng/ml. The incidence of adverse effects increases when serum concentrations exceed 2 ng/ml. The concentration causing adverse reactions increases with the duration of exposure. The tendency to develop tolerance shows considerable inter-individual variety.

Paediatric population

The safety of transdermal fentanyl was evaluated in three open-label trials in 293 paediatric patients with chronic pain, 2 years of age through to 18 years of age, of which 66 children were aged to 2 to 6 years. In these studies, 30 mg to 44 mg oral morphine per day was replaced by one fentanyl 12.5 microgram/hour transdermal patch. Starting dose of 25 microgram/hour and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg of oral morphine.

5.2 Pharmacokinetic properties

A release membrane controls the transdermal delivery of fentanyl. Transdermal diffusion occurs at a relatively even speed for 72 hours following the application of the transdermal patch.

Absorption

After the first application of fentanyl transdermal patches, serum fentanyl concentrations increase gradually, generally levelling off between 12 and 24 hours, and remaining relatively constant for the remainder of the 72-hour application period. The serum fentanyl concentrations attained are dependent on the fentanyl transdermal patch size. For all practical purposes by the second 72-hour application, a steady state serum concentration is reached and is maintained during subsequent applications of a patch of the same size.

Distribution

The plasma protein binding for fentanyl is 84%.

Biotransformation

Fentanyl is metabolised primarily in the liver via CYP3A4. The major metabolite, norfentanyl, is inactive.

Elimination

Fentalis Reservoir 25 microgram/hour Transdermal Patches - (... http://www.medicines.org.uk/emc/print-document?documentId=...

When treatment with fentanyl transdermal patches is withdrawn, serum fentanyl concentrations decline gradually, falling approximately 50% in 13-22 hours in adults or 22-25 hours in children, respectively. Continued absorption of fentanyl from the skin accounts for a slower reduction in serum concentration than is seen after an intravenous infusion.

Around 75% of fentanyl is excreted into the urine, mostly as metabolites, with less than 10% as unchanged active substance. About 9% of the dose is recovered in the faeces, primarily as metabolites.

Pharmacokinetics in special populations

Older people

Data from intravenous studies with fentanyl suggest that older patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the active substance than younger patients. In a study conducted with a fentanyl transdermal patch, healthy older subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Older patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.2).

Paediatric population

Adjusting for body weight, clearance (L/hour/Kg) in paediatric patients appears to be 82% higher in children 2 to 5 years old and 25% higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are likely to have the same clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients.

Hepatic impairment

In a study conducted with patients with hepatic cirrhosis, the pharmacokinetics of a single 50 microgram/hour application were assessed. Although t_{max} and $t_{1/2}$ were not altered, the mean plasma C_{max} and AUC values increased by approximately 35% and 73%, respectively, in these patients. Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of Fentalis Reservoir transdermal patches reduced if necessary (see section 4.4).

Renal impairment

Data obtained from a study administering intravenious fentanyl in patients undergoing renal transplantation suggest that the clearance of fentanyl may be reduced in this patient population. If patients with renal impairment receive Fentalis Reservoir transdermal patches, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity.

In a rat study fentanyl did not influence male fertility. Studies with female rats revealed reduced fertility and enhanced embryonal mortality. More recent studies showed that effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. There were no indications for teratogenic effects in studies in two species. In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed.

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumours at subcutaneous doses up to 33 microgram/kg/day in males or 100 microgram/kg/day in females. The overall exposure ($AUC_{0-24\,h}$) achieved in this study was <40% of that likely to be achieved clinically at the dose strength of 100 microgram/hour fentanyl transdermal patch, due to the maximum tolerated plasma concentrations in rats.

6. Pharmaceutical particulars

6.1 List of excipients

Occlusive backing:	polyethylene-terephthalate/ethylenvinylacetate-copolymer
Drug reservoir:	ethanol 96 %
	hydroxyethylcellulose
	purified water
Release membrane:	ethylenvinylacetate-copolymer
Adhesive surface:	silicone medical adhesive

Protective layer (remove before patch application):polyethylene-terephthalate, release coated

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package. Do not refrigerate or freeze.

6.5 Nature and contents of container

The transdermal patch is individually packaged in a protective sachet foil paper/PE/Al/PE.

Packages containing 3, 5, 7, 10, 14 and 20 transdermal patches

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Please refer to section 4.2 for instructions on how to apply the patch. There are no safety and pharmacokinetic data available for other application sites.

Significant quantities of fentanyl remain in the transdermal patches even after use. After removal, the used transdermal patches shouldbe folded in half adhesive side inwards so that the adhesive is not exposed, placed in the original sachet and then discarded safely out of the sight and reach of children. Unused patches should be returned to the pharmacy.

Wash hands with water only after applying or removing the patch.

7. Marketing authorisation holder

Sandoz Limited

Frimley Business Park,

Frimley,

Camberley,

Surrey,

GU16 7SR.

United Kingdom

8. Marketing authorisation number(s)

PL 04416/0744

9. Date of first authorisation/renewal of the authorisation

14/06/2007

10. Date of revision of the text

21/05/2015

Company Contact Details

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 **For use with question 13:**

Adrenal suppression

During prolonged therapy with corticosteroids, particularly with systemic use, adrenal atrophy develops and can persist for years after stopping. Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension, or death.

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary reintroduction of corticosteroid treatment. To avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period, anaesthetists **must** know whether a patient is taking or has been taking a corticosteroid. A suitable regimen for corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of surgery, is:

- Minor surgery under general anaesthesia—usual oral corticosteroid dose on the morning of surgery or hydrocortisone (usually the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery.
- Moderate or major surgery—usual oral corticosteroid dose on the morning of surgery and hydrocortisone intravenously at induction, followed by hydrocortisone 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual pre-operative oral corticosteroid dose is recommenced on stopping hydrocortisone injections.

Patients on long-term corticosteroid treatment should carry a steroid treatment card which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

ALFACALCIDOL

Show all parts of this monograph

Indications and dose

Hypophosphataemic rickets,
Persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism

By mouth, or by intravenous injection

For Child 1 month–11 years
25–50 nanograms/kg once daily, dose to be adjusted as necessary; maximum 1 microgram per day.

For Child 12–17 years
1 microgram once daily, dose to be adjusted as necessary.

Persistent neonatal hypocalcaemia

By mouth, or by intravenous injection

For Neonate
50–100 nanograms/kg once daily, dose to be adjusted as necessary, in resistant cases higher doses may be needed; increased if necessary up to 2 micrograms/kg daily.

Prevention of vitamin D deficiency in renal or cholestatic liver disease

By mouth, or by intravenous injection

For Neonate
20 nanograms/kg once daily, dose to be adjusted as necessary.

For Child 1 month–11 years (body-weight up to 20 kg)
15–30 nanograms/kg once daily (max. per dose 500 nanograms).

For Child 1 month–11 years (body-weight 20 kg and above)
250–500 nanograms once daily, dose to be adjusted as necessary.

For Child 12–17 years
250–500 nanograms once daily, dose to be adjusted as necessary.

Dose equivalence and conversion

One drop of alfacalcidol 2 microgram/mL oral drops contains approximately 100 nanograms alfacalcidol.

Contra-indications

For all VITAMIN D AND ANALOGUES (SYSTEMIC)

Hypercalcaemia; metastatic calcification

Cautions

Nephrolithiasis; take care to ensure correct dose in infants

Interactions

Individual interactants:

- Alfacalcidol (/interaction/alfacalcidol-2.html)

Side-effects

For all VITAMIN D AND ANALOGUES (SYSTEMIC)

Overdose

Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine.

For ALFACALCIDOL

Rare

Nephrocalcinosis; pruritus; rash; urticaria

Pregnancy

For all VITAMIN D AND ANALOGUES (SYSTEMIC)

High doses teratogenic in *animals* but therapeutic doses unlikely to be harmful.

Breast feeding

For all VITAMIN D AND ANALOGUES (SYSTEMIC)

Caution with high doses; may cause hypercalcaemia in infant—monitor serum-calcium concentration.

Renal impairment

Monitoring

Monitor plasma-calcium concentration in renal impairment.

Monitoring requirements

For all VITAMIN D AND ANALOGUES (SYSTEMIC)

Monitoring of patient parameters

Important: All patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occur.

For ALFACALCIDOL

Monitoring of patient parameters

Monitor plasma-calcium concentration in patients receiving high doses.

Directions for administration

With intravenous use

For injection, shake ampoule for at least 5 seconds before use, and give over 30 seconds.

Medicinal forms

There can be variation in the licensing of different medicines containing the same drug.

Forms available from special-order manufacturers include: oral suspension, oral solution

Solution for injection, Oral drops, Capsule (../medicinal-forms/alfacalcidol.html)

Related Treatment Summaries

- Minerals (../treatment-summary/minerals.html)
- Short bowel syndrome (../treatment-summary/short-bowel-syndrome.html)
- Vitamins (../treatment-summary/vitamins.html)

Other drugs in the class vitamin d and analogues

- CALCIPOTRIOL (/drug/calcipotriol.html)
- CALCIPOTRIOL WITH BETAMETHASONE (/drug/calcipotriol-with-betamethasone.html)
- CALCITRIOL (/drug/calcitriol.html)
- COLECALCIFEROL (/drug/colecalciferol.html)
- COLECALCIFEROL WITH CALCIUM CARBONATE (/drug/colecalciferol-with-calcium-carbonate.html)
- COLECALCIFEROL WITH CALCIUM PHOSPHATE (/drug/colecalciferol-with-calcium-phosphate.html)
- ERGOCALCIFEROL (/drug/ergocalciferol.html)
- ERGOCALCIFEROL WITH CALCIUM LACTATE AND CALCIUM PHOSPHATE (/drug/ergocalciferol-with-calcium-lactate-and-calcium-phosphate.html)
- TACALCITOL (/drug/tacalcitol.html)

For use with question 18,*please turn over*:

Package Leaflet: Information for the user

Concerta® XL 18 mg Prolonged Release Tablets
Concerta® XL 36 mg Prolonged Release Tablets
Concerta® XL 54 mg Prolonged Release Tablets

Methylphenidate hydrochloride

The name of your medicine is Concerta XL, it contains the active substance 'methylphenidate hydrochloride'. The name 'methylphenidate' will also be used in this leaflet.

Important things you need to know about your medicine

This medicine is used to treat ADHD
- The full name for ADHD is 'Attention Deficit Hyperactivity Disorder'.
- The medicine helps with your brain activity. It can help improve your attention, help you concentrate, and make you less impulsive.
- You need to have other treatments for ADHD as well as this medicine.

Read Section 1 for more information.

Before you take this medicine, talk to your doctor if:
- You have heart, circulation, or mental health problems - you may not be able to take this medicine.
- You are taking any other medicines - this is because methylphenidate can affect how other medicines work.

Read Section 2 for more information.

While taking this medicine:
- See your doctor regularly. This is because your doctor will want to check how the medicine is working.
- Do not stop taking the medicine without first talking to your doctor.
- Your doctor may stop your medicine to see if it is still needed, if you take it for more than a year.
- The most common side effects are feeling nervous, not being able to sleep or having a headache.

Read Sections 3 and 4 for more information.

Talk to your doctor straight away if any of the following happen:
- Your mood and how you feel changes.
- You feel any problems with your heart.

Read Section 4 for more information.

The rest of this leaflet includes more detail and other important information on the safe and effective use of this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

The leaflet has been written in sections:

- Sections 1 to 6 are for parents and carers (sometimes called 'your guardians').
- The last section is a special section for a child or young person to read.

However, all sections are written as though the child or young person taking the medicine is reading them.

The sections are:

Now read the rest of this leaflet before you start taking this medicine because it contains important information for you.

1 What Concerta XL is and what it is used for

What it is used for

Concerta XL is used to treat 'attention deficit hyperactivity disorder' (ADHD).
- it is used in children and young people between the ages of 6 and 18.
- it is used only after trying treatments which do not involve medicines. Such as counselling and behavioural therapy.

Concerta XL is not for use as a treatment for ADHD in children under 6 years of age or for the initiation of treatment in adults. When treatment was started at a younger age, it might be appropriate to continue taking Concerta XL when you become an adult. Your doctor will advise you about this.

How it works

Concerta XL improves the activity of certain parts of the brain which are under-active. The medicine can help improve attention (attention span), concentration and reduce impulsive behaviour.
The medicine is given as part of a treatment programme, which usually includes:
- psychological
- educational and
- social therapy.

It is prescribed only by doctors who have experience in children or young people's behaviour problems. Although there is no cure for ADHD, it can be managed using treatment programmes.

About ADHD

Children and young people with ADHD find it:
- hard to sit still and
- hard to concentrate.

It is not their fault that they cannot do these things.
Many children and young people struggle to do these things. However, with ADHD they can cause problems with everyday life. Children and young people with ADHD may have difficulty learning and doing homework. They find it hard to behave well at home, at school or in other places.
ADHD does not affect the intelligence of a child or young person.

2 What you need to know before you take Concerta XL

Do not take Concerta XL if:
- you are allergic to methylphenidate or any of the other ingredients of this medicine (listed in section 6)
- you have a thyroid problem
- you have increased pressure in your eye (glaucoma)
- you have a tumour of your adrenal gland (phaeochromocytoma)
- you have an eating problem when you do not feel hungry or want to eat - such as 'anorexia nervosa'
- you have very high blood pressure or narrowing of the blood vessels, which can cause pain in the arms and legs
- you have ever had heart problems - such as a heart attack, uneven heartbeat, pain and discomfort in the chest, heart failure, heart disease or were born with a heart problem
- you have had a problem with the blood vessels in your brain - such as a stroke, swelling and weakening of part of a blood vessel (aneurysm), narrow or blocked blood vessels, or inflammation of the blood vessels (vasculitis)
- you are currently taking or have taken within the last 14 days an antidepressant (known as a monoamine oxidase inhibitor)- see 'Other medicines and Concerta XL'
- you have mental health problems such as:
  - a 'psychopathic' or 'borderline personality' problem
  - abnormal thoughts or visions or an illness called 'schizophrenia'
  - signs of a severe mood problem like:
    - o feeling like killing yourself
    - o severe depression, where you feel very sad, worthless and hopeless
    - o mania, where you feel unusually excitable, over-active, and un-inhibited.

Do not take methylphenidate if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before you take methylphenidate. This is because methylphenidate can make these problems worse.

Warnings and precautions

Talk to your doctor before taking Concerta XL if:
- you have liver or kidney problems
- you have a problem with swallowing or swallowing whole tablets
- you have a narrowing or blockage of your gut or food-pipe
- you have had fits (seizures, convulsions, epilepsy) or any abnormal brain scans (EEGs)
- you have ever abused or been dependent on alcohol, prescription medicines or street drugs
- you are a girl and have started your periods (see the 'Pregnancy, breast-feeding and contraception' section below)
- you have hard-to-control, repeated twitching of any parts of the body or you repeat sounds and words
- you have high blood pressure
- you have a heart problem which is not in the 'Do not take' section above
- you have a mental health problem which is not in the 'Do not take' section above.

Other mental health problems include:
- mood swings (from being manic to being depressed - called 'bipolar disorder')
- starting to be aggressive or hostile, or your aggression gets worse
- seeing, hearing or feeling things that are not there (hallucinations)
- believing things that are not true (delusions)
- feeling unusually suspicious (paranoia)
- feeling agitated, anxious or tense
- feeling depressed or guilty.

Tell your doctor or pharmacist if any of the above apply to you before starting treatment. This is because methylphenidate can make these problems worse. Your doctor will want to monitor how the medicine affects you.

Checks that your doctor will make before you start taking Concerta XL

These checks are to decide if methylphenidate is the correct medicine for you.
Your doctor will talk to you about:
- any other medicines you are taking
- whether there is any family history of sudden unexplained death
- any other medical problems (such as heart problems) you or your family may have
- how you are feeling, such as feeling high or low, having strange thoughts or if you have had any of these feelings in the past
- whether there is a family history of 'tics' (hard-to-control, repeated twitching of any parts of the body or repeating sounds and words)
- any mental health or behaviour problems you or other family members have ever had. Your doctor will discuss whether you are at risk of having mood swings (from being manic to being depressed - called 'bipolar disorder'). They will check your mental health history, and check if any of your family have a history of suicide, bipolar disorder or depression.

It is important that you provide as much information as you can. This will help your doctor decide if methylphenidate is the correct medicine for you. Your doctor may decide that other medical tests are needed before you start taking this medicine.

Other medicines and Concerta XL

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Do not take methylphenidate if you:
- are taking a medicine called a 'monoamine oxidase inhibitor' (MAOI) used for depression, or have taken an MAOI in the last 14 days. Taking an MAOI with methylphenidate may cause a sudden increase in your blood pressure.

If you are taking other medicines, methylphenidate may affect how well they work or may cause side effects. If you are taking any of the following medicines, check with your doctor or pharmacist before taking methylphenidate:
- other medicines for depression
- medicines for severe mental health problems
- medicines for epilepsy
- medicines used to reduce or increase blood pressure
- some cough and cold remedies which contain medicines that can affect blood pressure. It is important to check with your pharmacist when you buy any of these products
- medicines that thin the blood to prevent blood clots.

If you are in any doubt about whether any medicines you are taking are included in the list above, ask your doctor or pharmacist before taking methylphenidate.

Please tell you doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Having an operation

Tell your doctor if you are going to have an operation. You should not take methylphenidate on the day of your surgery if a certain type of anaesthetic is used. This is because there is a chance of a sudden rise in blood pressure during the operation.

Drug testing

This medicine may give a positive result when testing for drug use. This includes testing used in sport.

Concerta XL with alcohol

Do not drink alcohol while taking this medicine. Alcohol may make the side effects of this medicine worse. Remember that some foods and medicines contain alcohol.

Pregnancy, breast-feeding and contraception

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
It is not known if methylphenidate will affect an unborn baby. Tell your doctor or pharmacist before using methylphenidate if you are:
- having sex. Your doctor will discuss contraception with you
- pregnant or think you may be pregnant. Your doctor will decide whether you should take methylphenidate.
- breast-feeding or planning to breast-feed. It is possible that methylphenidate is passed into human breast milk. Therefore, your doctor will decide whether you should breast-feed while taking methylphenidate.

Driving and using machines

You may feel dizzy, have problems focussing or have blurred vision when taking methylphenidate. If these happen it may be dangerous to do things such as drive, use machines, ride a bike or horse or climb trees.
This medicine can affect your ability to drive. Do not drive whilst taking this medicine until you know how this medicine affects you. It may be an offence to drive if your ability to drive safely is affected. There is further information for patients who are intending to drive in Great Britain – go to https://www.gov.uk/drug-driving-law.

turn over

Information for children and young people

This info is to help you learn the main things about your medicine called Concerta XL.

If you don't enjoy reading, someone like your mum, dad or carer (sometimes called 'your guardian') can read it to you and answer any questions.

It may help if you read small bits at a time.

Why have I been given this medicine?

This medicine can help children and young people with 'ADHD'.
- ADHD can make you:
  - run about too much
  - not be able to pay attention
  - act quickly without thinking about what will happen next (impulsive).
- It affects learning, making friends and how you think about yourself. It is not your fault.

While you are taking this medicine
- as well as taking this medicine you will also get help with ways to cope with your ADHD such as talking to ADHD specialists.
- this medicine should help you. But it does not cure ADHD.
- you will need to go to your doctor several times a year for check ups. This is to make sure the medicine is working and that you are growing and developing OK.
- if you take the medicine for more than one year, your doctor may stop your medicine to see if it is still needed. This will probably happen in a school holiday.
- do not drink alcohol. Alcohol may make the side effects of this medicine worse.
- if you are having sex, please talk to your doctor about contraception. Girls must tell their doctor straight away if they think they may be pregnant. We do not know how this medicine affects unborn babies.

Some people cannot have this medicine

You cannot have this medicine if:
- you have a problem with your heart
- you feel very unhappy, depressed or have a mental illness.

turn over

Concerta XL contains lactose

This medicine contains lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

3 How to take Concerta XL

How much to take

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- your doctor will usually start treatment with a low dose and increase it gradually as required.
- the maximum daily dose is 54 mg.
- you should take Concerta XL once each day in the morning with a glass of water. The tablet should be swallowed whole and not chewed, broken, or crushed. The tablet may be taken with or without food.

The tablet does not dissolve completely after all of the drug has been released and sometimes the tablet shell may appear in your stools. This is normal.

If you do not feel better after 1 month of treatment

If you do not feel better, tell your doctor. They may decide you need a different treatment.

Not using Concerta XL properly

If Concerta XL is not used properly, this may cause abnormal behaviour. It may also mean that you start to depend on the medicine. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.

This medicine is only for you. Do not give this medicine to anyone else, even if their symptoms seem similar.

If you take more Concerta XL than you should

If you take too much medicine, talk to a doctor or call an ambulance straight away. Tell them how much has been taken.

Signs of overdose may include: being sick, feeling agitated, shaking, increased uncontrolled movements, muscle twitching, fits (may be followed by coma), feeling very happy, being confused, seeing, feeling or hearing things that are not real (hallucinations), sweating, flushing, headache, high fever, changes in heart beat (slow, fast or uneven), high blood pressure, dilated pupils and dry nose and mouth.

If you forget to take Concerta XL

Do not take a double dose to make up for a forgotten dose. If you forget a dose, wait until it is time for the next dose.

If you stop taking Concerta XL

If you suddenly stop taking this medicine, the ADHD symptoms may come back or unwanted effects such as depression may appear. Your doctor may want to gradually reduce the amount of medicine taken each day, before stopping it completely. Talk to your doctor before stopping Concerta XL.

Things your doctor will do when you are on treatment

Your doctor will do some tests

- before you start - to make sure that Concerta XL is safe and will be of benefit.
- after you start - they will be done at least every 6 months, but possibly more often. They will also be done when the dose is changed.
- these tests will include:
  - checking your appetite
  - measuring height and weight
  - measuring blood pressure and heart rate
  - checking whether you have any problems with your mood, state of mind or any other unusual feelings. Or if these have got worse while taking Concerta XL.

Long-term treatment

Concerta XL does not need to be taken for ever. If you take Concerta XL for more than a year, your doctor should stop treatment for a short time, this may happen during a school holiday. This will show if the medicine is still needed.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Although some people get side effects, most people find that methylphenidate helps them. Your doctor will talk to you about these side effects.

Some side effects could be serious. If you have any of the side effects below, see a doctor straight away:

Common (may affect up to 1 in 10 people)

- uneven heartbeat (palpitations)
- mood changes or mood swings or changes in personality

Uncommon (may affect up to 1 in 100 people)

- thinking about or feeling like killing yourself
- seeing, feeling, or hearing things that are not real, these are signs of psychosis
- uncontrolled speech and body movements (Tourette's)
- signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing

Rare (may affect up to 1 in 1,000 people)

- feeling unusually excited, over-active and un-inhibited (mania)

Very rare (may affect up to 1 in 10,000 people)

- heart attack
- sudden death
- suicidal attempt
- fits (seizures, convulsions epilepsy)
- skin peeling or purplish red patches
- inflammation or blocked arteries in the brain
- muscle spasms which you cannot control affecting your eyes, head, neck, body and nervous system -due to a temporary lack of blood supply to the brain
- decrease in number of blood cells (red cells, white cells and platelets) which can make you more likely to get infections, and make you bleed and bruise more easily
- a sudden increase in body temperature, very high blood pressure and severe convulsions ('Neuroleptic Malignant Syndrome'). It is not certain that this side effect is caused by methylphenidate or other drugs that may be taken in combination with methylphenidate.

Not known (frequency cannot be estimated from the available data)

- unwanted thoughts that keep coming back
- unexplained fainting, chest pain, shortness of breath (these can be signs of heart problems)
- paralysis or problems with movement and vision, difficulties in speech (these can be signs of problems with the blood vessels in your brain)

If you have any of the side effects above, see a doctor straight away.

Other side effects include the following, if they get serious, please tell your doctor or pharmacist:

Very common (may affect more than 1 in 10 people)

- headache
- feeling nervous
- not being able to sleep.

Common (may affect up to 1 in 10 people)

- joint pain
- blurred vision
- tension headache
- dry mouth, thirst
- trouble falling asleep
- high temperature (fever)
- problems with sex drive
- unusual hair loss or thinning
- muscle tightness, muscle cramps
- loss of appetite or decreased appetite
- inability to develop or maintain an erection
- itching, rash or raised red itchy rashes (hives)
- feeling unusually sleepy or drowsy, feeling tired
- clenching or grinding your teeth, feeling of panic
- tingling feeling, prickling, or numbness of the skin
- increased alanine aminotransferase (liver enzyme) level in your blood
- cough, sore throat or nose and throat irritation; upper respiratory tract infection; sinus infection
- high blood pressure, fast heart beat (tachycardia)
- dizziness (vertigo), feeling weak, movements which you cannot control, being unusually active
- feeling aggressive, agitated, anxious, depressed, irritable, tense, jittery and abnormal behaviour
- upset stomach or indigestion, stomach pain, diarrhoea, feeling sick, stomach discomfort and being sick.

Uncommon (may affect up to 1 in 100 people)

- dry eyes
- constipation
- chest discomfort
- blood in the urine
- listlessness
- shaking or trembling
- increased need to pass urine
- muscle pain, muscle twitching
- shortness of breath or chest pain
- feeling hot
- increases in liver test results (seen in a blood test)
- anger, feeling restless or tearful, talking too much, excessive awareness of surroundings, problems sleeping.

Rare (may affect up to 1 in 1,000 people)

- feeling disorientated or confused
- trouble seeing or double vision
- swelling of the breasts in men
- excessive sweating, redness of the skin, red raised skin rash.

Very rare (may affect up to 1 in 10,000 people)

- muscle cramps
- small red marks on the skin
- abnormal liver function including liver failure and coma
- changes in test results – including liver and blood tests
- abnormal thinking, lack of feeling or emotion, doing things over and over again, being obsessed with one thing
- fingers and toes feeling numb, tingling and changing colour (from white to blue, then red) when cold ('Raynaud's phenomenon').

Not known (frequency cannot be estimated from the available data)

- migraine
- dilated pupils
- very high fever
- slow, fast or extra heart beats
- a major fit ('grand mal convulsions')
- believing things that are not true
- severe stomach pain, often with feeling and being sick

Effects on growth

When used for more than a year, methylphenidate may cause reduced growth in some children. This affects less than 1 in 10 children.

- there may be lack of weight gain or height growth.
- your doctor will carefully watch your height and weight, as well as how well you are eating.
- if you are not growing as expected, then your treatment with methylphenidate may be stopped for a short time.

Reporting of side effects

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

In the UK you can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

In Ireland you can also report side effects directly via: HPRA Pharmacovigilance,

Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, E-mail: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Concerta XL

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Keep the bottle tightly closed in order to protect from moisture. Do not store above 30°C.

The pack contains one or two silica gel pouches. These pouches are used to keep the tablets dry and should not be eaten.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6 Contents of the pack and other information

What Concerta XL contains

The active substance is methylphenidate hydrochloride

- Concerta XL 18mg Prolonged Release Tablets contain 18mg of methylphenidate hydrochloride.
- Concerta XL 36mg Prolonged Release Tablets contain 36mg of methylphenidate hydrochloride.
- Concerta XL 54mg Prolonged Release Tablets contain 54mg of methylphenidate hydrochloride.

The other ingredients are:

- butylhydroxytoluene (E321), cellulose acetate, hypromellose (E464), phosphoric acid concentrated, poloxamer 188, polyethylene oxides 200K and 7000K, povidone K29-32, sodium chloride, stearic acid, succinic acid, iron oxide black (E172), iron oxide yellow (E172), and iron oxide red (E172, 54 mg tablet only).
- **Film coat:** hypromellose (E464), lactose monohydrate, titanium dioxide (E171), triacetin, iron oxide yellow (E172, 18 mg and 54 mg tablets only), iron oxide red (E172, 54 mg tablet only) and stearic acid (18 mg tablet only).
- **Clear coat:** carnauba wax, hypromellose (E464), macrogol 400.
- **Printing Ink:** iron oxide black (E172), hypromellose (E464), isopropyl alcohol, propylene glycol and purified water.

What Concerta XL looks like and contents of the pack

Concerta XL is available in four strengths: 18 mg, 27 mg, 36 mg and 54 mg. Each capsule shaped tablet is individually marked to aid identification:

- 18 mg: Yellow, with 'alza 18' printed on one side in black ink.
- 27 mg : Grey with 'alza 27' printed on one side with black ink.
- 36 mg: White with 'alza 36' printed on one side in black ink.
- 54 mg: Brownish-red with 'alza 54' printed on one side in black ink.

The medicinal product is available in bottles containing 28 or 30 prolonged-release tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:
Janssen-Cilag Ltd, 50-100 Holmers Farm Way, High Wycombe, Bucks, HP12 4EG, UK.

Manufacturer:
Janssen Pharmaceutica NV, Turnhoutseweg 30, 2340, Beerse, Belgium.

This leaflet was last revised in 03/2015

For information in large print, tape, CD or Braille, phone 0800 7318450 (UK) or 1800709122 (Ireland).

Some people need to talk to their doctor before they start having this medicine

You need to talk to your doctor if:

- you have epilepsy (fits)
- you are pregnant or breastfeeding
- you are taking other medicines – your doctor needs to know about all the medicines you are taking.

How do I take my medicine?

- swallow your medicine with water.
- your doctor will tell you how many times a day you should take your medicine
- do not stop taking the medicine without talking to your doctor first.

Possible side effects

Side effects are the unwanted things that can happen when you take a medicine. If any of the following happen, tell an adult you trust straight away. They can then talk to your doctor. The main things that could affect you are:

- feeling worried or nervous
- feeling dizzy, or getting head aches
- being very depressed and unhappy or wanting to hurt yourself
- having different moods than usual, not being able to get to sleep
- skin rashes, bruising easily, getting out of breath
- the medicine can also make you feel **sleepy**. If you feel sleepy, it is important **not to do outdoor sports** like riding a horse or bike, swimming or climbing trees. You could hurt yourself and others.
- your heart beating faster than usual.

If you feel unwell in any way while you are taking your medicine please tell an adult you trust straight away.

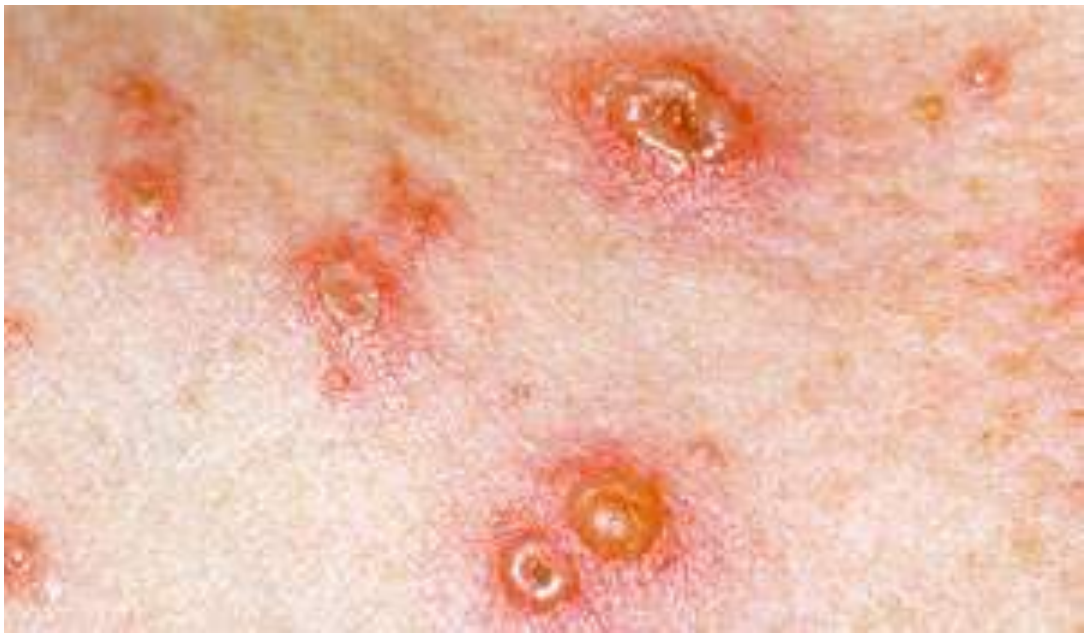
Other things to remember

- make sure you keep your medicine in a safe place, so that no one else takes it, especially younger brothers or sisters.
- the medicine is special for you - **do not let anyone else have it.** It may help you, but it could hurt someone else.
- if you forget to take your medicine **don't** take two tablets the next time. Just take one tablet at the next normal time.
- if you do take too much medicine, tell your mum, dad or carer **right away.**
- it is important not to take too much medicine or you will get ill.
- don't stop taking your medicine until your doctor says it's OK.

Who should I ask if there is anything I don't understand?

Your mum, dad, carer, doctor, nurse or pharmacist will be able to help you.

For use with question 21:



For use with question 24:

Test	Result	Reference Range
Serum sodium (mmol/L)	139	137-145
Serum potassium (mmol/L)	5.1	3.5-5.1
Serum urea (mmol/L)	6.2	2.5-7.5
Serum creatinine (µmol/L)	132	46-92
Estimated GFR (mL/min/1.73m^2)	41	> 60

For use with question 33:

Mr R. Coweley BSc. M.R.C.V.S
Veterinary Practice
87 Great Yarmouth Street
Midlands
RR4 8UI
Tel No: 5558 999 000

Date: *Today's date*

For Dolly the cat
Weighs: 24kg

Animal Owner: Ms P
35 Chester Gardens
Midlands

Rx Phenobarbital 30 mg tablets
1 daily
60 (sixty) tablets

The item has been prescribed for an animal or herd under the care of the veterinarian.

Signed: 

For use with question 36*:*

Self-monitoring of blood glucose

Frequency of self-monitoring of blood glucose

1.6.10 Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least 4 times a day, including before each meal and before bed. **[new 2015]**

1.6.11 Support adults with type 1 diabetes to test at least 4 times a day, and up to 10 times a day if any of the following apply:

- the desired target for blood glucose control, measured by HbA1c level (see recommendation 1.6.6), is not achieved
- the frequency of hypoglycaemic episodes increases
- there is a legal requirement to do so (such as before driving, in line with the Driver and Vehicle Licensing Agency [DVLA] At a glance guide to the current medical standards of fitness to drive)
- during periods of illness
- before, during and after sport
- when planning pregnancy, during pregnancy and while breastfeeding (see the NICE guideline on diabetes in pregnancy)
- if there is a need to know blood glucose levels more than 4 times a day for other reasons (for example, impaired awareness of hypoglycaemia, high-risk activities). **[new 2015]**

1.6.12 Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time, undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycaemia. **[new 2015]**

For use with question 37, *please turn over:*

Ensure® Twocal (Abbott)

Previous

Not suitable for use in child under 1 year; not recommended for child 1–6 years

Liquid (sip or tube feed) per 100 mL

Energy 838 kJ (200 kcal)

Protein 8.4 g, cows' milk

Carbohydrate 21 g, (sugars 4.5 g)

Fat 8.9 g

Fibre 1 g

Special characteristics Gluten-free. Residual lactose

ACBS Indications Standard; *also* haemodialysis, CAPD

Presentation and flavour Bottle: 200 mL = £2.22. Banana, neutral, strawberry, vanilla

Jevity® Promote (Abbott)

Previous Next

Liquid (tube feed) per 100 mL

Energy 434 kJ (103 kcal)

Protein 5.55 g, caseinates, soy isolates

Carbohydrate 12 g, (sugars 670 mg)

Fat 3.32 g

Fibre 1.7 g

Special characteristics Gluten-free. Residual lactose

ACBS Indications Standard. Not suitable for child under 2 years; not recommended for child 2–10 years

Presentation and flavour Flexible pack: 1000 mL = £10.80

Fresubin® 1000 Complete (Fresenius Kabi)

Previous

Not suitable for use in child under 1 year; not recommended for child 1–6 years

Liquid (tube feed) per 100 mL

Energy 420 kJ (100 kcal)

Protein 5.5 g, cows' milk

Carbohydrate 12.5 g, (sugars 1.1 g)

Fat 3.1 g

Fibre 2 g

Special characteristics Gluten-free. Residual lactose. Contains fish oil

ACBS Indications Standard

Presentation and flavour Flexible pack: 1000 mL = £10.56

Fresubin® Energy (Fresenius Kabi)

Previous Next

Not suitable for use in child under 1 year; not recommended for child 1–6 years

Liquid (sip feed) per 100 mL

Energy 630 kJ (150 kcal)

Protein 5.6 g, cows' milk

Carbohydrate 18.8 g, (sugars(1))

Fat 5.8 g

Fibre Nil

Special characteristics Gluten-free(2). Residual lactose. Contains fish gelatin

ACBS Indications Standard

Presentation and flavour Bottle: 200 mL = £1.48. Banana, black currant, cappuccino, chocolate, lemon, neutral, strawberry, tropical fruits, vanilla

Liquid (tube feed) per 100 mL

Energy 630 kJ (150 kcal)

Protein 5.6 g, cows' milk

Carbohydrate 18.8 g, (sugars 1.4 g)

Fat 5.8 g

Fibre Nil

Special characteristics Gluten-free. Residual lactose. Contains fish oil and fish gelatin

ACBS Indications Standard

Presentation and flavour Flexible pack: 500 mL = £5.05, 1000 mL = £9.92, 1500 mL = £13.30

Previous Next

[1] Sugar content varies with flavour

[2] Strawberry flavour may contain traces of wheat starch and egg

Novasource® GI Forte (Nestlé)

Previous

Not suitable for use in child under 1 year; not recommended for child 1–6 years

Liquid (tube feed) per 100 mL

Energy 631 kJ (150 kcal)

Protein 6 g, cows' milk

Carbohydrate 18.3 g, (sugars 1.8 g)

Fat 5.9 g

Fibre 2.2 g

Special characteristics Gluten-free. Residual lactose

ACBS Indications Standard

Presentation and flavour Flexible pack: 500 mL = £5.39, 1000 mL = £10.44

Nutrison® MCT (Nutricia Clinical)

Previous

Not suitable for use in child under 1 year; not recommended for child 1–6 years

Liquid (tube feed) per 100 mL

Energy 420 kJ (100 kcal)

Protein 5 g, cows' milk

Carbohydrate 12.6 g, (sugars 1 g)

Fat 3.3 g, (MCT 61%)

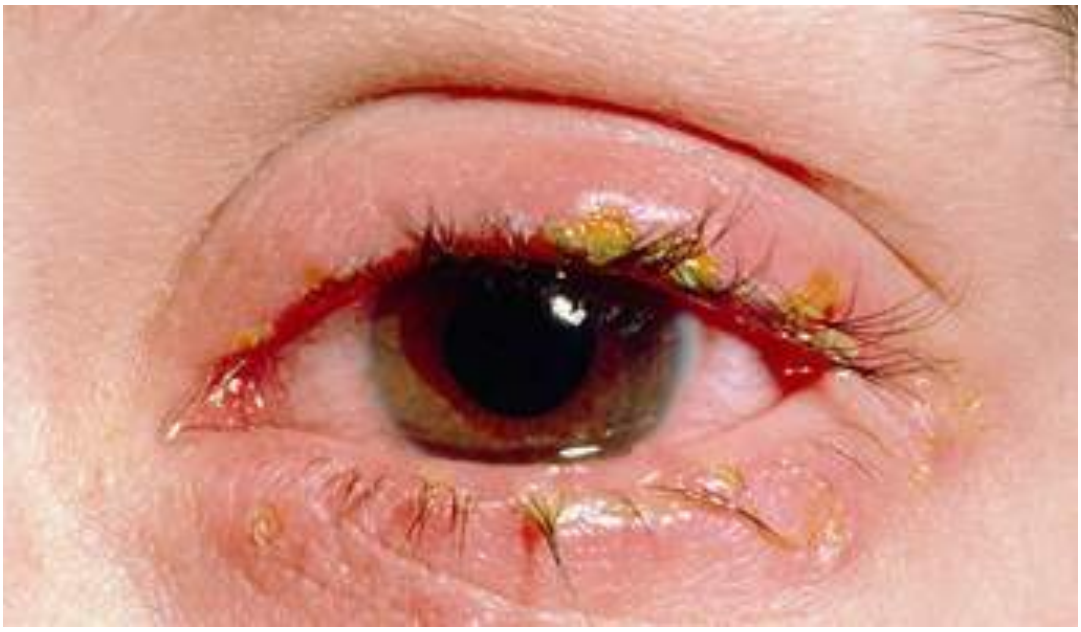
Fibre Nil

Special characteristics Gluten-free. Residual lactose

ACBS Indications Standard

Presentation and flavour Flexible pack: 1000 mL = £9.80

For use with question 39:



For use with question 41:

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.

For use with question 44:

ADRENALINE/EPINEPHRINE

Emergency treatment of acute anaphylaxis (under expert supervision), Angioedema (if laryngeal oedema is present) (under expert supervision)

By intramuscular injection

For Child 1 month–5 years
150 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, suitable syringe to be used for measuring small volume; injected preferably into the anterolateral aspect of the middle third of the thigh.

For Child 6–11 years
300 micrograms, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, to be injected preferably into the anterolateral aspect of the middle third of the thigh.

For Child 12–17 years
500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function, 300 micrograms (0.3 mL) to be administered if child small or prepubertal.

For Adult
500 micrograms, to be injected preferably into the anterolateral aspect of the middle third of the thigh, doses may be repeated several times if necessary at 5 minute intervals according to blood pressure, pulse, and respiratory function.