ProPharmace Pre-registration Training

PROPHARMACE MOCK REGISTRATION ASSESSMENT 2020
Part 2
RESOURCE PACK

Instructions to candidates

1. This resource pack is available to use for questions 1, 4, 10, 12, 14, 17, 18, 22, 28, 31, 34, 48, 52, 55, 57, 58, 59, 66, 72, 74, 79, 84, 95, 96, 97, 109, 110, 111, 119 and 120.
2. A table of contents is shown on page 2 and 3 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

48	Accessed from https://www.nhs.uk/conditions	26
52	Accessed from https://www.medicines.org.uk/emc/files/pil.10313.pdf	27
55	Accessed from https://bnf.nice.org.uk/guidance/prescribing-in-palliative-care.html	29
57+58	Accessed from https://www.medicines.org.uk/emc/product/1681/smpc	30
59	Veterinary prescription	35
66	Accessed from https://bnf.nice.org.uk/drug/mefloquine.html#indicationsAndDoses	36
72	Baby scalp condition	39
74	Accessed from https://www.medicines.org.uk/emc/product/5696/smpc	40
79	FP10 Prescription	44
84	Accessed from https://www.medicines.org.uk/emc/product/1655/smpc	45
95+96+97	Accessed from https://www.medicines.org.uk/emc/product/7936	51
109	FP10 Prescription	64
110	FP10 Prescription	65
111	FP10 Prescription	66
119+120	Accessed from https://bnf.nice.org.uk/wound-management/	67

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

MANAGEMENT OF COMMUNITY ACQUIRED PNEUMONIA IN ADULTS

Table 5 Initial empirical treatment regimens for community acquired pneumonia (CAP) in adults

Pneumonia severity (based on clinical judgement supported by CURB65 severity score)	Treatment site	Preferred treatment	Alternative treatment
Low severity (eg, CURB65 = 0–1 or CRB-65 = 0, <3% mortality)	Home	Amoxicillin 500 mg tds orally	Doxycycline 200 mg loading dose then 100 mg orally *or* clarithromycin 500 mg bd orally
Low severity (eg, CURB65 = 0–1, <3% mortality) but admission indicated for reasons other than pneumonia severity (eg, social reasons/unstable comorbid illness)	Hospital	Amoxicillin 500 mg tds orally If oral administration not possible: amoxicillin 500 mg tds IV	Doxycycline 200 mg loading dose then 100 mg od orally *or* clarithromycin 500 mg bd orally
Moderate severity (eg, CURB65 = 2, 9% mortality)	Hospital	Amoxicillin 500 mg – 1.0g tds orally *plus* clarithromycin 500 mg bd orally If oral administration not possible: amoxicillin 500 mg tds IV or benzylpenicillin 1.2 g qds IV *plus* clarithromycin 500 mg bd IV	Doxycycline 200 mg loading dose then 100 mg orally or levofloxacin 500 mg od orally *or* moxifloxacin 400 mg od orally*
High severity (eg, CURB65 = 3–5, 15–40% mortality)	Hospital (consider critical care review)	**Antibiotics given as soon as possible** Co-amoxiclav 1.2 g tds IV plus clarithromycin 500 mg bd IV (If legionella strongly suspected, consider adding levofloxacin ¥)	Benzylpenicillin 1.2 g qds IV *plus* either levofloxacin 500 mg bd IV *or* ciprofloxacin 400 mg bd IV OR Cefuroxime 1.5 g tds IV or cefotaxime 1 g tds IV or ceftriaxone 2 g od IV, plus clarithromycin 500 mg bd IV (If legionella strongly suspected, consider adding levofloxacin ¥)

bd, twice daily; IV, intravenous; od, once daily; qds, four times daily; tds, three times daily.

*Following reports of an increased risk of adverse hepatic reactions associated with oral moxifloxacin, in October 2008 the European Medicines Agency (EMEA) recommended that moxifloxacin "should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection".

¥ Caution – risk of QT prolongation with macrolide-quinolone combination.

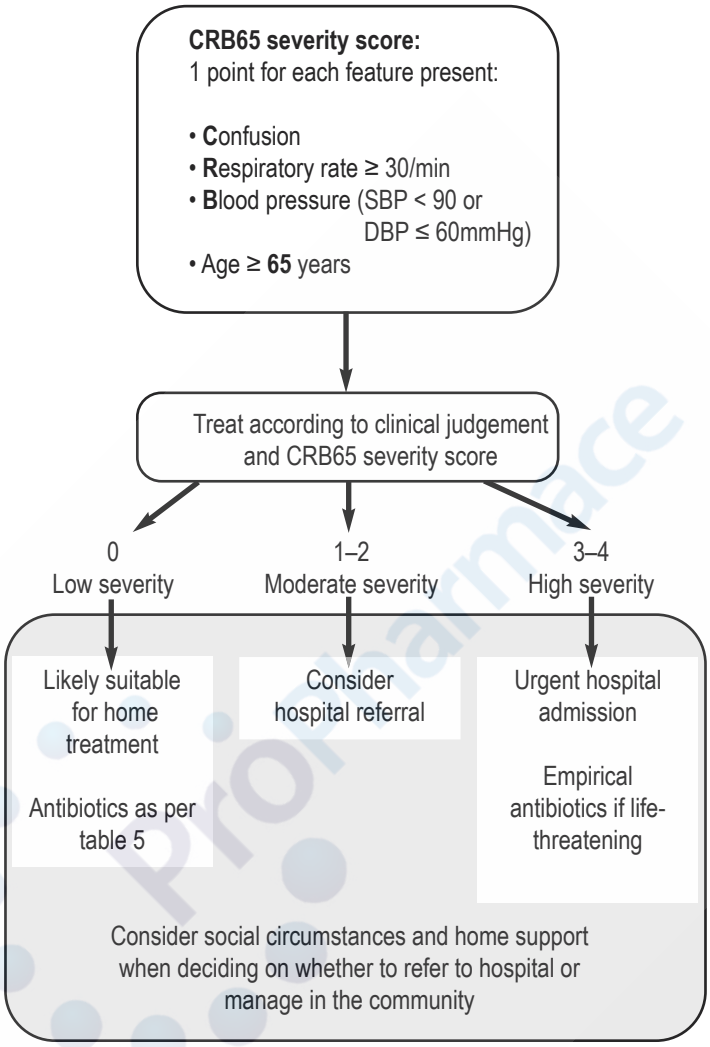
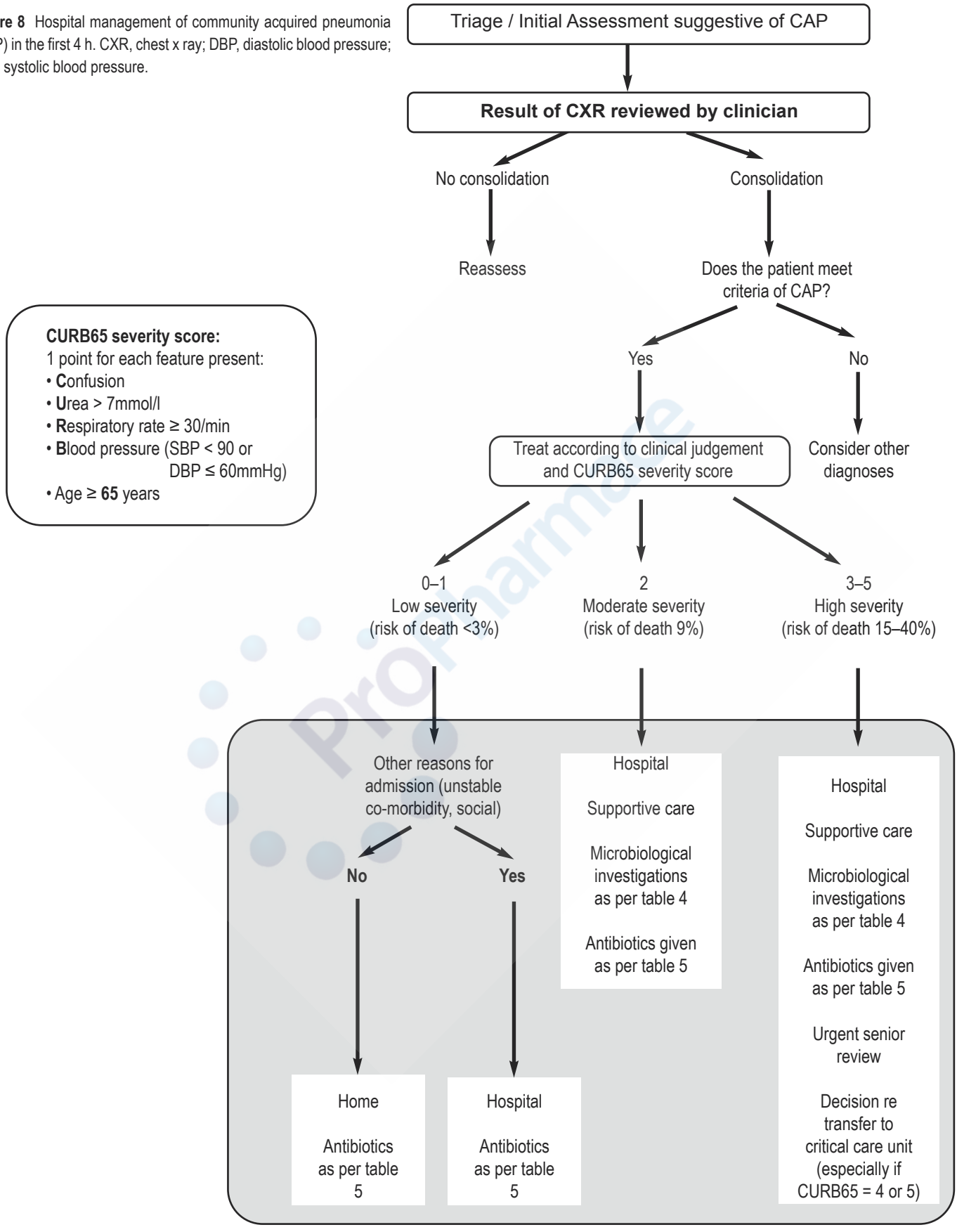


Figure 7 Severity assessment of community acquired pneumonia (CAP) in patients seen in the community (CRB65 severity score plus clinical judgement). DBP, diastolic blood pressure; SBP, systolic blood pressure.

Figure 8 Hospital management of community acquired pneumonia (CAP) in the first 4 h. CXR, chest x ray; DBP, diastolic blood pressure; SBP, systolic blood pressure.



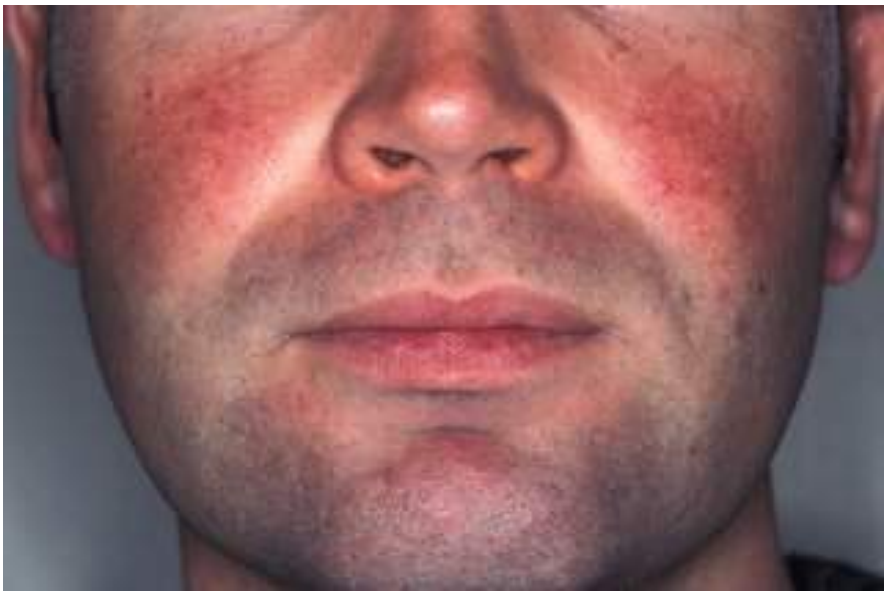
Aim by 4 hours: diagnosis made and management including antibiotics started

For use with question 4:

Iron content of different iron salts

Iron salt/amount	Content of ferrous iron
ferrous fumarate 200 mg	65 mg
ferrous gluconate 300 mg	35 mg
ferrous sulfate 300 mg	60 mg
ferrous sulfate, dried 200 mg	65 mg

For use with question 10:



NICE National Institute for Health and Care Excellence

HYDROCORTISONE

Drug action

Hydrocortisone has equal glucocorticoid and mineralocorticoid activity.

Indications and dose

For HYDROCORTISONE

Thyrotoxic crisis (thyroid storm)

By intravenous injection

For Adult
100 mg every 6 hours, to be administered as sodium succinate.

Adrenocortical insufficiency resulting from septic shock

By intravenous injection

For Adult
50 mg every 6 hours, given in combination with fludrocortisone.

Acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylaxis (adjunct to adrenaline)

By intravenous injection

For Adult
100–300 mg, to be administered as sodium succinate.

Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of minor surgery under general anaesthesia

By intravenous injection, or by intravenous infusion

For Adult
Initially 25–50 mg, to be administered at induction of surgery, the patient's usual oral corticosteroid dose is recommenced after surgery.

Corticosteroid replacement, in patients who have taken more than 10 mg prednisolone daily (or equivalent) within 3 months of moderate or major surgery

Initially by intravenous injection, or by intravenous infusion

For Adult
Initially 25–50 mg, to be administered at induction of surgery (following usual oral corticosteroid dose on the morning of surgery), followed by (by intravenous injection) 25–50 mg 3 times a day for 24 hours after moderate surgery and for 48–72 hours after major surgery.

Adrenocortical insufficiency in Addison's disease or following adrenalectomy

By mouth using immediate-release medicines

For Adult
20–30 mg daily in 2 divided doses, the larger dose to be given in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion, the optimum daily dose is determined on the basis of clinical response.

Adrenocortical insufficiency

By intramuscular injection, or by slow intravenous injection, or by intravenous infusion

For Adult
100–500 mg 3–4 times a day or when required.

Severe inflammatory bowel disease

By slow intravenous injection, or by intravenous infusion

For Adult
100–500 mg 3–4 times a day or when required.

Replacement in adrenocortical insufficiency

By mouth using modified-release medicines

For Adult
20–30 mg once daily, adjusted according to response, dose to be taken in the morning.

By mouth using immediate-release medicines

For Adult
20–30 mg daily in divided doses, adjusted according to response.

Ulcerative colitis, Proctitis, Proctosigmoiditis

By rectum using rectal foam

For Adult
Initially 1 metered application 1–2 times a day for 2–3 weeks, then reduced to 1 metered application once daily on alternate days, to be inserted into the rectum.

Acute hypersensitivity reactions, Angioedema

By intramuscular injection, or by intravenous injection

For Child 1–5 months
Initially 25 mg 3 times a day, adjusted according to response.

For Child 6 months–5 years
Initially 50 mg 3 times a day, adjusted according to response.

For Child 6–11 years
Initially 100 mg 3 times a day, adjusted according to response.

For Child 12–17 years
Initially 200 mg 3 times a day, adjusted according to response.

Mild inflammatory skin disorders such as eczemas

To the skin

For Child
Apply 1–2 times a day, to be applied thinly.

For Adult
Apply 1–2 times a day, to be applied thinly.

Nappy rash

To the skin

For Child
Apply 1–2 times a day for no longer than 1 week, discontinued as soon as the inflammation subsides.

Severe acute asthma,
Life-threatening acute asthma

By intravenous injection

For Child 1 month–1 year
4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 25 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate.

For Child 2–4 years
4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 50 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate.

For Child 5–11 years
4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 100 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate.

For Child 12–17 years
4 mg/kg every 6 hours (max. per dose 100 mg), alternatively 100 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate.

For Adult
100 mg every 6 hours until conversion to oral prednisolone is possible, dose given, preferably, as sodium succinate.

Oral and perioral lesions

To the lesion using buccal tablet

For Child 1 month–11 years
Only on medical advice.

For Child 12–17 years
1 lozenge 4 times a day, allowed to dissolve slowly in the mouth in contact with the ulcer.

For Adult
1 lozenge 4 times a day, allowed to dissolve slowly in the mouth in contact with the ulcer.

Local treatment of conjunctival inflammation (short-term)

To the eye

For Adult
Apply 2 drops 2–4 times a day for up to 14 days, to avoid relapse, frequency may be gradually reduced to once every other day.

Side-effects

For all CORTICOSTEROIDS (SYSTEMIC)

Common or very common

Anxiety; behaviour abnormal; cataract subcapsular; cognitive impairment; Cushing's syndrome; electrolyte imbalance; fatigue; fluid retention; gastrointestinal discomfort; headache; healing impaired; hirsutism; hypertension; increased risk of infection; menstrual cycle irregularities; mood altered; nausea; osteoporosis; peptic ulcer; psychotic disorder; skin reactions; sleep disorders; weight increased

Uncommon

Adrenal suppression; alkalosis hypokalaemic; appetite increased; bone fractures; diabetic control impaired; eye disorders; glaucoma; haemorrhage; heart failure; hyperhidrosis; hypotension; leucocytosis; myopathy; osteonecrosis; pancreatitis; papilloedema; seizure; thromboembolism; tuberculosis reactivation; vertigo; vision blurred

Rare or very rare

Malaise; tendon rupture

Frequency not known

Chorioretinopathy; growth retardation (very common in children); intracranial pressure increased with papilloedema (usually after withdrawal); telangiectasia

Side-effects, further information

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. 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.

Infections

Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. septicaemia and tuberculosis may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis

may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated.

Chickenpox

Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox. Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunisation with varicella–zoster immunoglobulin is needed for exposed non–immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment. Corticosteroids should not be stopped and dosage may need to be increased.

Measles

Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Psychiatric reactions

Systemic corticosteroids, particularly in high doses, are linked to psychiatric reactions including euphoria, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions, and behavioural disturbances. These reactions frequently subside on reducing the dose or discontinuing the corticosteroid but they may also require specific management. Patients should be advised to seek medical advice if psychiatric symptoms (especially depression and suicidal thoughts) occur and they should also be alert to the rare possibility of such reactions during withdrawal of corticosteroid treatment. Systemic corticosteroids should be prescribed with care in those predisposed to psychiatric reactions, including those who have previously suffered corticosteroid–induced psychosis, or who have a personal or family history of psychiatric disorders.

For all CORTICOSTEROIDS (TOPICAL)

Common or very common

Skin reactions; telangiectasia

Rare or very rare

Adrenal suppression; hypertrichosis; skin depigmentation (may be reversible)

Frequency not known

Local reaction; vasodilation

For all CORTICOSTEROIDS (TOPICAL)

The potency of each topical corticosteroid should be included on the label with the directions for use. The label should be attached to the container (for example, the tube) rather than the outer packaging.

For HYDROCORTISONE

With topical use

When hydrocortisone cream or ointment is prescribed and no strength is stated, the 1% strength should be supplied.

Although *Dioderm*® contains only 0.1% hydrocortisone, the formulation is designed to provide a clinical activity comparable to that of Hydrocortisone Cream 1% BP.

In children

The RCPCH and NPPG recommend that, when a liquid special of hydrocortisone is required, the following strength is used: 5 mg/5 mL.

Patient and carer advice

For all CORTICOSTEROIDS (SYSTEMIC)

Patient resources

Advice for patients

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.

A patient information leaflet should be supplied to every patient when a systemic corticosteroid is prescribed. Patients should especially be advised of the following:

- **Immunosuppression** Prolonged courses of corticosteroids can increase susceptibility to infection and serious infections can go unrecognised. Unless already immune, patients are at risk of severe **chickenpox** and should avoid close contact with people who have chickenpox or shingles. Similarly, precautions should also be taken against contracting **measles**;
- **Adrenal suppression** If the corticosteroid is given for longer than 3 weeks, treatment must not be stopped abruptly. Adrenal suppression can last for a year or more after stopping treatment and the patient must mention the course of corticosteroid when receiving treatment for any illness or injury;
- **Mood and behaviour changes** Corticosteroid treatment, especially with high doses, can alter mood and behaviour early in treatment—the patient can become confused, irritable and suffer from delusion and suicidal thoughts. These effects can also occur when corticosteroid treatment is being withdrawn. Medical advice should be sought if worrying psychological changes occur;

For use with question 14, *please turn over*:

Isotretinoin 20mg capsules

Summary of Product Characteristics Updated 30-Apr-2019 | Alliance Pharmaceuticals

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. Name of the medicinal product

Isotretinoin 20mg Capsules

Rizuderm 20mg Capsules

2. Qualitative and quantitative composition

Each capsule contains 20mg isotretinoin.

Excipients with known effect:

Contains soya bean oil (refined, hydrogenated and partially hydrogenated) maltitol and sorbitol.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsules, soft.

Red/orange soft capsules marked 'P20'.

4. Clinical particulars

Some of the side effects associated with the use of isotretinoin are related to the dose. The side effects are generally reversible after changing the dose or stopping treatment, however some may continue after treatment has stopped.

4.1 Therapeutic indications

Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring), resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

4.2 Posology and method of administration

Posology

Isotretinoin should only be prescribed by or under the supervision of physicians with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.

The capsules should be taken with food once or twice daily.

Paediatric population

Isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended in patients less than 12 years of age due to a lack of data on efficacy and safety.

Adults including adolescents and the elderly:

Isotretinoin therapy should be started at a dose of 0.5 mg/kg daily. The therapeutic response to isotretinoin and some of the adverse effects are dose-related and vary between patients. This necessitates individual dosage adjustment during therapy. For most patients, the dose ranges from 0.5-1.0 mg/kg per day.

Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120-150 mg/kg. The duration of treatment will depend on the individual daily dose. A treatment course of 16-24 weeks is normally sufficient to achieve remission.

In the majority of patients, complete clearing of the acne is obtained with a single treatment course. In the event of a definite relapse a further course of isotretinoin therapy may be considered using the same daily dose and cumulative treatment dose. As further improvement of the acne can be observed up to 8 weeks after discontinuation of treatment, a further course of treatment should not be considered until at least this period has elapsed.

Patients with renal impairment

In patients with severe renal insufficiency treatment should be started at a lower dose (e.g. 10 mg/day). The dose should then be increased up to 1 mg/kg/day or until the patient is receiving the maximum tolerated dose (see section 4.4 "Special warnings and special precautions for use").

Patients with intolerance

In patients who show severe intolerance to the recommended dose, treatment may be continued at a lower dose with the consequences of a longer therapy duration and a higher risk of relapse. In order to achieve the maximum possible

efficacy in these patients the dose should normally be continued at the highest tolerated dose.

4.3 Contraindications

Isotretinoin is contraindicated in women who are pregnant or breastfeeding. (see section 4.6 "Fertility, pregnancy and lactation").

Isotretinoin is contraindicated in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (see section 4.4 "Special warnings and special precautions for use").

Isotretinoin is also contraindicated in patients with hypersensitivity to isotretinoin or to any of the excipients listed in section 6.1. This medicine contains hydrogenated soya-bean oil and refined soya-bean oil. Therefore, this product is contraindicated in patients who are allergic to peanuts or soya.

Isotretinoin is also contraindicated in patients:

• With hepatic insufficiency

• With excessively elevated blood lipid values

• With hypervitaminosis A

• Receiving concomitant treatment with tetracyclines (see section 4.5 "Interaction with other medicinal products and other forms of interactions")

4.4 Special warnings and precautions for use

Teratogenic effects

Isotretinoin is a powerful human teratogen inducing a high frequency of severe and life threatening birth defects.

Isotretinoin is strictly contraindicated in:

- Pregnant women

-Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met

Pregnancy Prevention Programme

This medicinal product is TERATOGENIC

Isotretinoin is contraindicated in women of childbearing potential unless all of the following conditions of the Pregnancy Prevention Programme are met:

• She has severe acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy (see section 4.1 "Therapeutic indications").

• The potential for pregnancy must be assessed for all female patients.

• She understands the teratogenic risk.

• She understands the need for rigorous follow-up, on a monthly basis.

• She understands and accepts the need for effective contraception, without interruption, 1 month before starting treatment, throughout the entire duration of treatment and for 1 month after the end of treatment. At least one highly effective method of contraception (i.e a user-independent form) or two complementary user-dependent forms should be used.

• Individual circumstances should be evaluated in each case, when choosing the contraception method, involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

• Even if she has amenorrhea she must follow all the advice on effective contraception.

• She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy or if she might be pregnant.

• She understands the need and accepts to undergo regular pregnancy testing before, ideally monthly during treatment and 1 month after stopping treatment.

• She has acknowledged that she has understood the hazards and necessary precautions associated with the use of isotretinoin.

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

The prescriber must ensure that:

• The patient complies with the conditions for pregnancy prevention as listed above, including confirmation that she has an adequate level of understanding.

• The patient has acknowledged the aforementioned conditions.

• The patient understands that she must consistently and correctly use one highly effective method of contraception (i.e. a user-independent form) or two complementary user-dependent forms of contraception, for at least 1 month prior to starting treatment and is continuing to use effective contraception throughout the treatment period and for at least 1 month after cessation of treatment.

• Negative pregnancy test results have been obtained before, during and 1 month after the end of treatment. The dates and results of pregnancy tests should be documented.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

If pregnancy occurs after stopping treatment there remains a risk of severe and serious malformation of the foetus. This risk persists until the product has been completely eliminated, which is within one month following the end of treatment.

Contraception

Female patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. If the prescribing physician is not in a position to provide such information the patient should be referred to the relevant healthcare professional.

As a minimum requirement, female patients of childbearing potential pregnancy must use at least one highly effective method of contraception (i.e. a user-independent form), or two complementary user-dependent forms of contraception. Contraception should be used for at least 1 month prior to starting treatment throughout treatment and continue for at least 1 month after stopping treatment with isotretinoin, even in patients with amenorrhea.

Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25mIU/mL are recommended to be performed, as follows.

Prior to starting therapy:

At least one month after the patient has started using contraception, and shortly (preferably a few days) prior to the first prescription, the patient should undergo a medically supervised pregnancy test. This test should ensure the patient is not pregnant when she starts treatment with isotretinoin.

Follow-up visits

Follow-up visits should be arranged at regular intervals, ideally monthly. The need for repeated medically supervised pregnancy tests every month should be determined according to local practice including consideration of the patient's sexual activity and recent menstrual history (abnormal menses, missed periods or amenorrhea) and method of contraception. Where indicated, follow-up pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

End of treatment

1 month after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy.

Prescribing and dispensing restrictions

For women of childbearing potential, the prescription duration of Isotretinoin capsules should ideally be limited to 30 days in order to support regular follow up, including pregnancy testing and monitoring. Ideally, pregnancy testing, issuing a prescription and dispensing of Isotretinoin capsules should occur on the same day. Dispensing of isotretinoin should occur within a maximum of 7 days of the prescription.

This monthly follow-up will allow ensuring that regular pregnancy testing and monitoring is performed and that the patient is not pregnant before receiving the next cycle of medication.

Male patients

The available data suggests that the level of maternal exposure from the semen of the patients receiving isotretinoin is not of a sufficient magnitude to be associated with the teratogenic effects of isotretinoin.

Male patients should be reminded that they must not share their medication with anyone, particularly not females.

Additional precautions

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy and for 1 month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

Educational material

In order to assist prescribers, pharmacists and patients in avoiding foetal exposure to isotretinoin the Marketing Authorisation Holder will provide educational material to reinforce the warnings about the teratogenicity of isotretinoin, to provide advice on contraception before therapy is started and to provide guidance on the need for pregnancy testing.

Full patient information about the teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to all patients, both male and female.

Psychiatric disorders

Depression, depression aggravated, anxiety, aggressive tendencies, mood alterations, psychotic symptoms and, very rarely, suicidal ideation, suicide attempts and suicide have been reported in patients treated with isotretinoin (see section 4.8 "Undesirable effects"). Particular care needs to be taken in patients with a history of depression and all patients should be monitored for signs of depression and referred for appropriate treatment if necessary.

However, discontinuation of isotretinoin may be insufficient to alleviate symptoms and therefore further psychiatric or psychological evaluation may be necessary.

Awareness by family or friends may be useful to detect mental health deterioration.

Skin and subcutaneous tissues disorders

Acute exacerbation of acne is occasionally seen during the initial period but this subsides with continued treatment, usually within 7-10 days, and usually does not require dose adjustment.

Exposure to intense sunlight or to UV rays should be avoided. Where necessary a sun-protection product with a high protection factor of at least SPF 15 should be used.

Aggressive chemical dermabrasion and cutaneous laser treatment should be avoided in patients on isotretinoin for a period of 5-6 months after the end of the treatment because of the risk of hypertrophic scarring in atypical areas and more rarely post inflammatory hyper or hypopigmentation in treated areas. Wax depilation should be avoided in patients on isotretinoin for at least a period of 6 months after treatment because of the risk of epidermal stripping.

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.

There have been post-marketing reports of severe skin reactions (e.g. erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) associated with isotretinoin use. As these events may be difficult to distinguish from other skin reactions that may occur (see section 4.8), patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If a severe skin reaction is suspected, isotretinoin treatment should be discontinued.

Allergic Reactions

Anaphylactic reactions have been rarely reported, in some cases after previous topical exposure to retinoids. Allergic cutaneous reactions are reported infrequently. Serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement have been reported. Severe allergic reactions necessitate interruption of therapy and careful monitoring.

Eye disorders

Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy.

Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Decreased night vision has also been reported and the onset in some patients was sudden (see section 4.7 "Effects on ability to drive and to use machines"). Patients experiencing visual difficulties should be referred for an expert ophthalmological opinion. Withdrawal of isotretinoin may be necessary.

Musculo-skeletal and connective tissue disorders

Myalgia, arthralgia and increased serum creatine phosphokinase values have been reported in patients receiving isotretinoin, particularly in those undertaking vigorous physical activity (see section 4.8 "Undesirable effects"). In some cases, this may progress to potentially life threatening rhabdomyolysis.

Bone changes including premature epiphyseal closure, hyperostosis, and calcification of tendons and ligaments have occurred after several years of administration at very high doses for treating disorders of keratinisation. The dose levels, duration of treatment and total cumulative dose in these patients generally far exceeded those recommended for the treatment of acne.

Benign intracranial hypertension

Cases of benign intracranial hypertension have been reported, some of which involved concomitant use of tetracyclines (see sections 4.3 "Contraindications" and 4.5 "Interactions with other medicinal products and other forms of interaction"). Signs and symptoms of benign intracranial hypertension include headache, nausea and vomiting, visual disturbances and papilloedema. Patients who develop benign intracranial hypertension should discontinue isotretinoin immediately.

Hepatobiliary disorders

Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases

have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.

Renal insufficiency

Renal insufficiency and renal failure do not affect the pharmacokinetics of isotretinoin. Therefore, isotretinoin can be given to patients with renal insufficiency. However, it is recommended that patients are started on a low dose and titrated up to the maximum tolerated dose (see section 4.2 "Posology and Method of Administration").

Lipid Metabolism

Serum lipids (fasting values) should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Elevated serum lipid values usually return to normal on reduction of the dose or discontinuation of treatment and may also respond to dietary measures.

Isotretinoin has been associated with an increase in plasma triglyceride levels. Isotretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see section 4.8 "Undesirable effects"). Levels in excess of 800mg/dL or 9mmol/L are sometimes associated with acute pancreatitis, which may be fatal.

Gastrointestinal disorders

Isotretinoin has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. Patients experiencing severe (haemorrhagic) diarrhoea should discontinue isotretinoin immediately.

Fructose intolerance

Isotretinoin capsules contain sorbitol and maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

High Risk Patients

In patients with diabetes, obesity, alcoholism or a lipid metabolism disorder undergoing treatment with isotretinoin, more frequent checks of serum values for lipids and/or blood glucose may be necessary. Elevated fasting blood sugars have been reported, and new cases of diabetes have been diagnosed during isotretinoin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should not take vitamin A as concurrent medication due to the risk of developing hypervitaminosis A.

Cases of benign intracranial hypertension (pseudotumor cerebri) have been reported with concomitant use of isotretinoin and tetracyclines. Therefore, concomitant treatment with tetracyclines must be avoided (see section 4.3 "Contraindications" and section 4.4 "Special warnings and special precautions for use").

Concurrent administration of isotretinoin with topical keratolytic or exfoliative anti-acne agents should be avoided as local irritation may increase (see section 4.4 Special warnings and special precautions for use).

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy is an absolute contraindication to treatment with isotretinoin (see section 4.3 "Contraindications"). Women of childbearing potential have to use effective contraception one month before, during and up to one month after treatment. If pregnancy does occur in spite of these precautions during treatment with isotretinoin or in the month following, there is a great risk of very severe and serious malformation of the foetus.

The foetal malformations associated with exposure to isotretinoin include central nervous system abnormalities (hydrocephalus, cerebellar malformation/abnormalities, microcephaly), facial dysmorphia, cleft palate, external ear abnormalities (absence of external ear, small or absent external auditory canals), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of great vessels, septal defects), thymus gland abnormality and parathyroid gland abnormalities. There is also an increased incidence of spontaneous abortion.

If pregnancy occurs in a woman treated with isotretinoin, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice.

Breast-feeding

Isotretinoin is highly lipophilic, therefore the passage of isotretinoin into human milk is very likely. Due to the potential for adverse effects in the child exposed via mothers' milk, the use of isotretinoin is contraindicated in nursing mothers.

Fertility

Isotretinoin, in therapeutic dosages, does not affect the number, motility and morphology of sperm and does not jeopardise the formation and development of the embryo on the part of the men taking isotretinoin.

4.7 Effects on ability to drive and use machines

Isotretinoin could potentially have an influence on the ability to drive and use machines. A number of cases of decreased night vision have occurred during isotretinoin therapy and in rare instances have persisted after therapy (see section 4.4 "Special warnings and special precautions for use" and section 4.8 "Undesirable effects"). Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating machines.

Drowsiness, dizziness and visual disturbances have been reported very rarely. Patients should be warned that if they experience these effects, they should not drive, operate machinery or take part in any other activities where the symptoms could put either themselves or others at risk.

4.8 Undesirable effects

Some of the side effects associated with the use of isotretinoin are dose-related. The side effects are generally reversible after altering the dose or discontinuation of treatment, however some may persist after treatment has stopped. The following symptoms are the most commonly reported undesirable effects with isotretinoin: dryness of the skin, dryness of the mucosae e.g. of the lips (cheilitis), the nasal mucosa (epistaxis) and the eyes (conjunctivitis).

Infections:	
Very Rare (≤1/10 000)	Gram positive (mucocutaneous) bacterial infection
Blood and lymphatic system disorders:	
Very common (≥1/10) Common (≥1/100, <1/10) Very Rare (≤1/10000)	Anaemia, Red blood cell sedimentation rate increased, Thrombocytopenia, Thrombocytosis Neutropenia Lymphadenopathy
Immune system disorders:	
Rare(≥1/10000,<1/1000)	Allergic skin reaction, Anaphylactic reactions, Hypersensitivity
Metabolism and nutrition disorders:	
Very Rare (≤1/10000)	Diabetes mellitus, Hyperuricaemia
Psychiatric disorders:	
Rare (≥1/10000,<1/1000) Very Rare (≤1/10000)	Depression, Depression aggravated, Aggressive tendencies, Anxiety, Mood alterations Abnormal behaviour, Psychotic disorder, Suicidal ideation, Suicide attempt, Suicide
Nervous system disorders:	
Common (≥1/100,<1/10) Very Rare (≤1/10 000)	Headache Benign intracranial hypertension, Convulsions, Drowsiness, Dizziness
Eye disorders:	
Very common (≥1/10) Very Rare (≤1/10000)	Blepharitis, Conjunctivitis, Dry eye, Eye irritation Blurred vision, Cataract, Colour blindness (colour vision deficiencies), Contact lens intolerance, Corneal opacity, Decreased night vision, Keratitis, Papilloedema (as sign of benign intracranial hypertension), Photophobia, Visual disturbances
Ear and labyrinth disorders:	
Very Rare (≤1/10 000)	Hearing impaired
Vascular disorders:	
Very Rare (≤1/10000)	Vasculitis (for example Wegener's granulomatosis, allergic vasculitis)

Respiratory, thoracic and mediastinal disorders:	
Common (≥1/100,<1/10) Very Rare (≤1/10000)	Epistaxis, Nasal dryness, Nasopharyngitis Bronchospasm (particularly in patients with asthma), Hoarseness
Gastrointestinal disorders:	
Very Rare (≤1/10000)	Colitis, Ileitis, Dry throat, Gastrointestinal haemorrhage, haemorrhagic diarrhoea and inflammatory bowel disease, Nausea, Pancreatitis (see section 4.4 "Special warnings and special precautions for use")
Hepatobiliary disorders:	
Very common (≥1/10) Very Rare (≤1/10000)	Transaminase increased (see section 4.4 "Special warnings and special precautions for use") Hepatitis
Skin and subcutaneous tissues disorders:	
Very common (≥1/10) Rare (≥l/10000,<l/1000) Very Rare (≤1/10 000) Frequency unknown*	Cheilitis, Dermatitis, Dry skin, Localised exfoliation, Pruritus, Rash erythematous, Skin fragility (risk of frictional trauma) Alopecia Acne fulminans. Acne aggravated (acne flare), Erythema (facial), Exanthema, Hair disorders, Hirsutism, Nail dystrophy, Paronychia, Photosensitivity reaction, Pyogenic granuloma, Skin hyperpigmentation, Sweating increased Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis.
Musculo-skeletal and connective tissue disorders:	
Very common (≥1/10) Very Rare (≤1/10 000) Frequency unknown*:	Arthralgia, myalgia, back pain (particularly in children and adolescent patients) Arthritis, Calcinosis (calcification of ligaments and tendons), Epiphyses premature fusion, Exostosis, (hyperostosis), Reduced bone density, Tendonitis Rhabdomyolysis
Renal and urinary disorders:	
Very Rare (≤1/10 000)	Glomerulonephritis
Reproductive system and breast disorders:	
Frequency unknown*	Sexual dysfunction including erectile dysfunction and decreased libido, Gynaecomastia
General disorders and administration site conditions:	
Very Rare (≤1/10 000)	Granulation tissue (increased formation of), Malaise
Investigations:	
Very common (≥1/10) Common (≥1/100, <1/10) Very Rare (≤1/10000)	Blood triglycerides increased, High density lipoprotein decreased Blood cholesterol increased, Blood glucose increased, Haematuria, Proteinuria Blood creatine phosphokinase increased

* cannot be estimated from the available data

Reporting of suspected adverse reactions

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

4.9 Overdose

Isotretinoin is a derivative of vitamin A. Although the acute toxicity of isotretinoin is low, signs of hypervitaminosis A could appear in cases of accidental overdose. Manifestations of acute vitamin A toxicity include severe headache, nausea or vomiting, drowsiness, irritability and pruritus. Signs and symptoms of accidental or deliberate overdosage with isotretinoin would probably be similar. These symptoms would be expected to be reversible and to subside without the need for treatment.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Retinoids for treatment of acne.

ATC code: D10BA01

Mechanism of action

Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established.

Clinical efficacy and safety

Hypercornification of the epithelial lining of the pilosebaceous unit leads to shedding of corneocytes into the duct and blockage by keratin and excess sebum. This is followed by formation of a comedone and, eventually, inflammatory lesions. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly program of differentiation. Sebum is a major substrate for the growth of Propionibacterium acnes so that reduced sebum production inhibits bacterial colonisation of the duct.

5.2 Pharmacokinetic properties

Absorption

The absorption of isotretinoin from the gastro-intestinal tract is variable and dose-linear over the therapeutic range. The absolute bioavailability of isotretinoin has not been determined, since the compound is not available as an intravenous preparation for human use, but extrapolation from dog studies would suggest a fairly low and variable systemic bioavailability. When isotretinoin is taken with food, the bioavailability is doubled relative to fasting conditions.

Distribution

Isotretinoin is extensively bound to plasma proteins, mainly albumin (99.9%).

The volume of distribution of isotretinoin in man has not been determined since isotretinoin is not available as an intravenous preparation for human use. In humans little information is available on the distribution of isotretinoin into tissue. Concentrations of isotretinoin in the epidermis are only half of those in serum. Plasma concentrations of isotretinoin are about 1.7 times those of whole blood due to poor penetration of isotretinoin into red blood cells.

Biotransformation

After oral administration of isotretinoin, three major metabolites have been identified in plasma: 4-oxo-isotretinoin, tretinoin, (all-trans retinoic acid), and 4-oxo-tretinoin. These metabolites have shown biological activity in several in vitro tests. 4-oxo-isotretinoin has been shown in a clinical study to be a significant contributor to the activity of isotretinoin (reduction in sebum excretion rate despite no effect on plasma levels of isotretinoin and tretinoin). Other minor metabolites includes glucuronide conjugates. The major metabolite is 4-oxo-isotretinoin with plasma concentrations at steady state that are 2.5 times higher than those of the parent compound.

Isotretinoin and tretinoin (all-trans retinoic acid) are reversibly metabolised (interconverted), and the metabolism of tretinoin is therefore linked with that of isotretinoin. It has been estimated that 20-30% of an isotretinoin dose is metabolised by isomerisation.

Enterohepatic circulation may play a significant role in the pharmacokinetics of isotretinoin in man. In vitro metabolism studies have demonstrated that several CYP enzymes are involved in the metabolism of isotretinoin to 4-oxo-isotretinoin and tretinoin. No single isoform appears to have a predominant role. Isotretinoin and its metabolites do not significantly affect CYP activity.

Elimination

After oral administration of radiolabelled isotretinoin approximately equal fractions of the dose were recovered in urine and faeces. Following oral administration of isotretinoin, the terminal elimination half-life of unchanged drug in patients with acne has a mean value of 19 hours. The terminal elimination half-life of 4-oxo-isotretinoin is longer, with a mean value of 29 hours.

Isotretinoin is a physiological retinoid and endogenous retinoid concentrations are reached within approximately two weeks following the end of isotretinoin therapy.

For use with question 17 and 18:

Biochemical test	Result	Target
Renal profile		
Serum sodium	141 mmol/L	133-146mmol/L
Serum potassium	4.7 mmol/L	3.5-5.3mmol/L
Serum creatinine	72 micromol/L	62-106 micromol/L
GFR calculated abbreviated MDRD	>90ml/min/1.73 square metres	>90ml/min/1.73 square metres
Serum Lipids		
Serum cholesterol	3.0 mmol/L	<5mmol/L
Serum triglyceride	0.7 mmol/L	<1.8mmol/L
Serum HDL cholesterol	1.89 mmol/L	1-4mmol/L
Serum LDL cholesterol	1.6 mmol/L	0-3mmol/L
Serum cholesterol/HDL ratio	2.7	0-5
HbA1c	41 mmol/mol	Diabetic control target 48-59mmol/mol; non diabetic control target 20-42 mmol/mol
Thyroid function test		
Serum TSH level	0.03mIU/L	0.27-4.20 mIU/L
Serum free T4 level	14.7pmol/L	12-22 pmol/L
Serum free T3 level	4.9pmol/L	3.1-6.8 pmol/L
Full blood count		
Haemoglobin estimation	120g/L	115-155 g/L
Red blood cell count	4.35x10 12/L	3.95-5.15

For use with question 22:

Pharmacy stamp *Please don't stamp over age box*	Age D.O.B	Title, Forename, Surname & Address Mr P 45 High Street W7 8LE NHS Number
Number of day's treatment		
Endorsements	Zolpidem 10mg tablets Take one daily as directed Quant 56	
Signature of Prescriber JR	Date 27/02/2020	
For Dispenser No. Of Prescns. on form	Dr Amazing 1234567 The Best Surgery 700 Lovely Street, WC1 1JN FP10	

For use with question 28:

For use with question 31: *The following resource has been extracted from the GOLD Guidelines:*

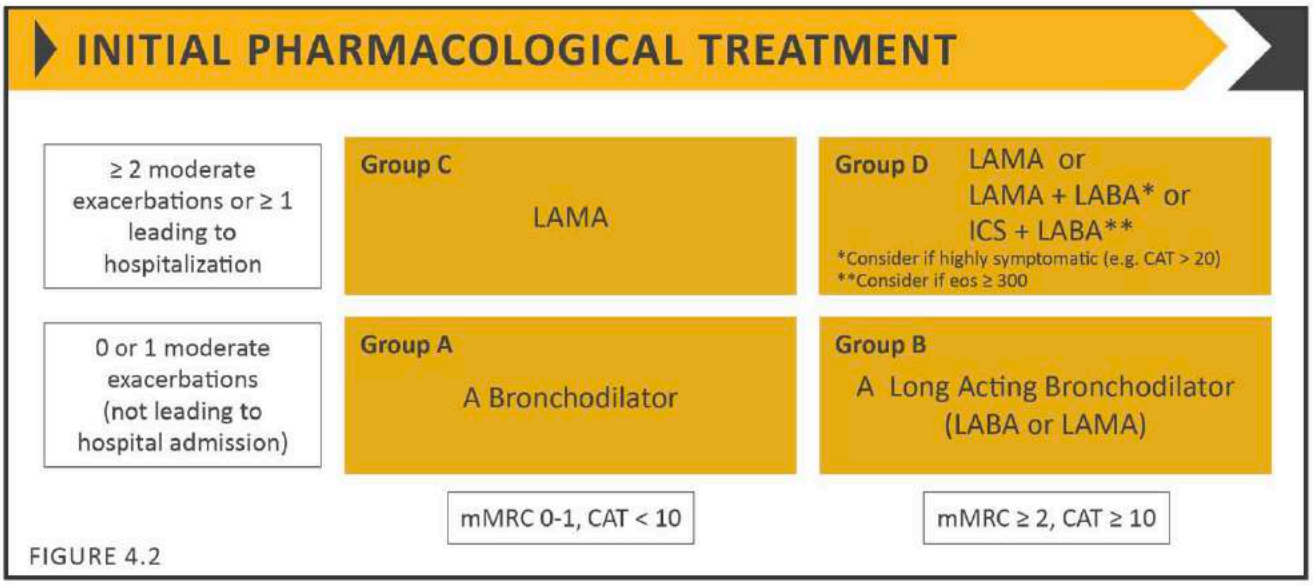


FIGURE 4.2

Definition of abbreviations: eos: blood eosinophil count in cells per microliter; mMRC: modified Medical Research Council dyspnea questionnaire; CAT™: COPD Assessment Test™.

Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment (**Figure 4.3**). Following review of the patient response to treatment initiation, adjustments in pharmacological treatment may be needed.

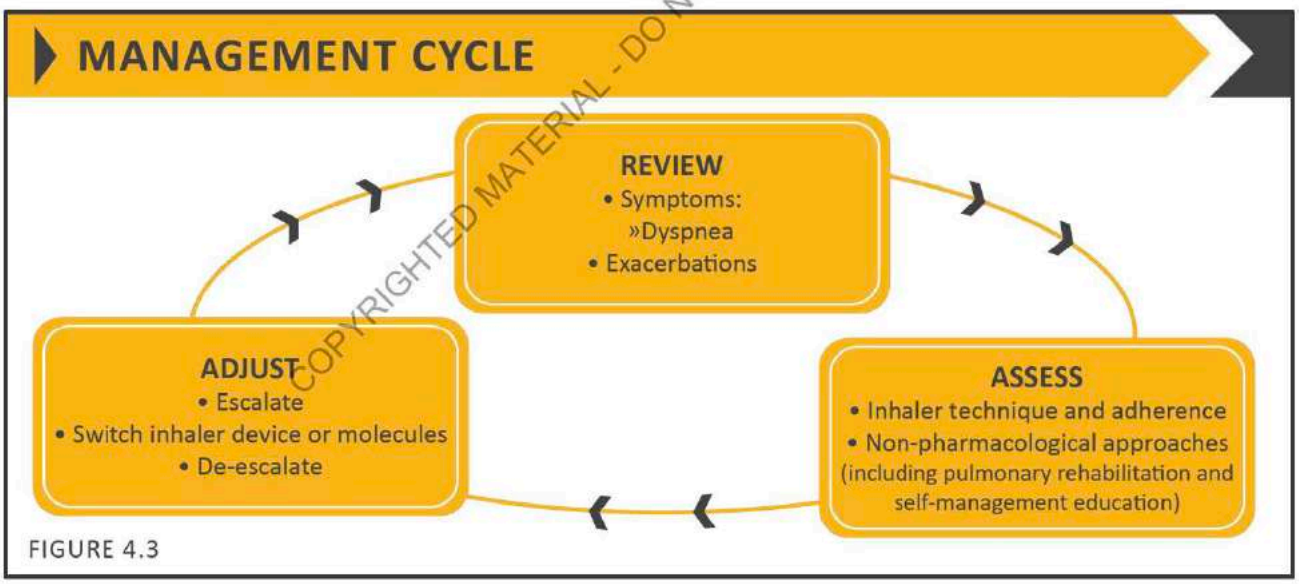
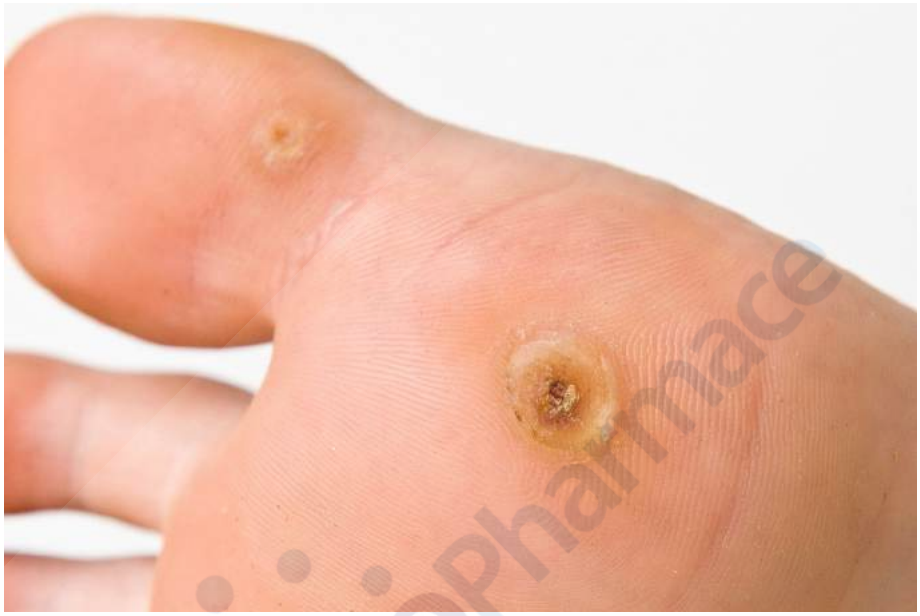


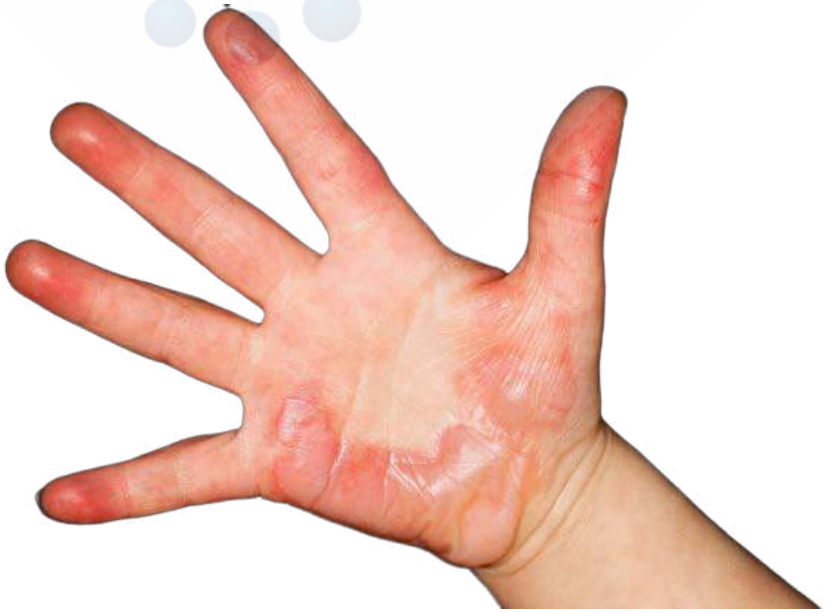
FIGURE 4.3

A separate algorithm is provided for **FOLLOW-UP** treatment, where the management is still based on symptoms and exacerbations, but the recommendations do not depend on the patient's GOLD group at diagnosis (**Figure 4.4**). These follow-up recommendations are designed to facilitate management of patients taking maintenance treatment(s), whether early after initial treatment or after years of follow-up. These recommendations incorporate recent evidence from clinical trials and the use of peripheral blood eosinophil counts as a biomarker to guide the use of ICS therapy for exacerbation prevention (see more detailed information regarding blood eosinophil counts as a predictor of ICS effects in **Chapter 3**).

For use with question 34:



For use with question 48:



Package leaflet: Information for the user

Levothyroxine 25 micrograms/5ml Oral Solution
Levothyroxine 50 micrograms/5ml Oral Solution
Levothyroxine 100 micrograms/5ml Oral Solution
Levothyroxine 125 micrograms/5ml Oral Solution

Levothyroxine sodium

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- 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.

What is in this leaflet

1. What Levothyroxine Oral Solution is and what it is used for

Levothyroxine Oral Solution contains levothyroxine which is used to treat hypothyroidism, a condition in which the thyroid gland is underactive and so does not make enough thyroxine for the body's needs.

Levothyroxine Oral Solution is also used to treat thyroid cancer and diffuse non toxic goitre or Hashimoto's thyroiditis, conditions in which the thyroid gland becomes enlarged causing a swelling in the front of the neck.

2. What you need to know before you take Levothyroxine Oral Solution

Do not take Levothyroxine Oral Solution:

- if you are allergic to levothyroxine or any of the other ingredients of this medicine (listed in section 6)
- if you suffer from underactive adrenal glands and you do not have adequate corticosteroid cover
- if you have a history of heart attack (acute myocardial infarction), inflammation of the heart muscle (acute myocarditis) or inflammation of the sac surrounding the heart (acute pericarditis)
- if you are pregnant do not take this medicine in combination with medicines to treat hyperthyroidism (see the section on Pregnancy and breast-feeding).

Warnings and precautions

Talk to your doctor before taking Levothyroxine Oral Solution:

- if you have heart disease, problems with your circulation or high blood pressure
- if you are suffering from an overactive thyroid gland (hyperthyroidism), an underactive adrenal gland, diabetes, or have had an underactive thyroid gland for some time.

Other medicines and Levothyroxine Oral Solution

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines without a prescription. Levothyroxine can interfere with the action of some other drugs and some drugs can have an effect on levothyroxine. In particular tell your doctor or pharmacist if you take the following drugs:

- medication to stop your blood clotting (for example warfarin)
- medication for depression (for example sertraline, imipramine, amitriptyline)
- medication for epilepsy (for example phenytoin, phenobarbital, carbamazepine)
- medication for diabetes
- rifampicin (for infections, particularly tuberculosis)
- digoxin or amiodarone (for your heart)
- propranolol (for high blood pressure), lovastatin (for high cholesterol levels) or phenylbutazone or aspirin (anti-inflammatory drugs)
- oestrogen, oestrogen containing products and oral contraceptives, androgens or corticosteroids
- sucralfate, cimetidine or aluminium hydroxide for a stomach ulcer, colestyramine to lower your cholesterol levels, or calcium carbonate or iron supplements
- chloroquine or proguanil for the prevention of malaria
- protease inhibitors (for example ritonavir, indinavir and lopinavir) used to treat HIV
- ritonavir (used to control HIV and chronic hepatitis C virus)
- sevelamer (used to treat high levels of phosphate in the blood in patients with renal failure)
- tyrosine kinase inhibitors (for example imatinib and sunitinib) used to treat cancer
- propylthiouracil (used to treat hyperthyroidism)
- beta-sympathomimetics (used to treat low blood pressure)
- glucocorticoids (steroid hormones used to treat adrenal insufficiency and other diseases)
- soy-containing products (these can decrease absorption of levothyroxine).

Let your doctor or pharmacist know. Levothyroxine Oral Solution can be taken with these medicines but not at the same time.

If you go into hospital to have an operation, tell the anaesthetist or the medical staff that you are taking Levothyroxine Oral Solution. It may react with an anaesthetic (ketamine) which you may be given before an operation.

Levothyroxine Oral Solution with food, drink and alcohol

You should take your Levothyroxine Oral Solution on an empty stomach, usually before breakfast.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant while taking this medicine your doctor will monitor you closely.

Driving and using machines

Levothyroxine Oral Solution is unlikely to affect your ability to drive or to operate machinery.

Levothyroxine Oral Solution contains sodium methyl parahydroxybenzoate and glycerol

Levothyroxine Oral Solution contains sodium methyl parahydroxybenzoate (E219) which may cause allergic reactions (possibly delayed). It also contains glycerol which may cause headache, stomach upset and diarrhoea.

3. How to take Levothyroxine Oral Solution

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Levothyroxine Oral Solution should be swallowed.

Your doctor will have decided what dose you should take each day depending on your condition. Your doctor will take blood samples at regular intervals to monitor your response to treatment.

If you are switching from the oral solution to the tablet version of levothyroxine or from the tablet version to the oral solution of levothyroxine your doctor will monitor you more closely.

Administration

You should take your Levothyroxine Oral Solution on an empty stomach, usually before breakfast. For hypothyroidism the usual daily dosages are:

Adults and children over 12 years:

The starting dose is 50 to 100 micrograms (mcg) a day, increasing by 25 to 50 micrograms every 3-4 weeks, until you are taking the right amount for your condition. The usual maintenance dose is 100 to 200 micrograms daily. For diffuse non toxic goitre or Hashimoto's thyroiditis the recommended dose is 50-200 micrograms (mcg) per day.

For the treatment of thyroid cancer the recommended dose is 150-300 micrograms (mcg) per day.

Older patients (over 50 years of age):

The starting dose is 12.5 micrograms (mcg) a day, increasing by 12.5 micrograms every 2 weeks until the correct dose is obtained. The usual final dose is between 50 and 200 micrograms daily. This dose also applies to patients with severe hypothyroidism, and to those with heart disease.

Children under 12 years:

The dose for children depends on their age or weight. They will be monitored to make sure they get the right dose. The following is a guide:

Age	Micrograms per kg bodyweight
Up to 1 month	5-10 micrograms
Over 1 month	5 micrograms

The duration of treatment is usually for life if you are being treated for hypothyroidism, non toxic diffuse goitre or Hashimoto's thyroiditis.

Please use the oral syringe provided to deliver your specific dose (see instructions below). The syringe can be used to measure your dose by drawing the liquid to the correct mark on the syringe. For example if your dose is 50 micrograms daily then the corresponding volume would be:

For the 25 micrograms/5ml strength – 2 x 5ml (10ml in total)

For the 50 micrograms/5ml strength – 5ml

For the 100 micrograms/5ml strength – 2.5 ml

For the 125 micrograms/5ml strength – 2 ml

Levothyroxine can be taken using an oral syringe.

How to use the oral syringe:

1. Shake the bottle well, making sure the cap is firmly on the bottle.
2. Remove the cap. Note: Keep the cap nearby to close the bottle after each use.
3. Push the plastic adaptor into the neck of the bottle. Note: The adaptor must always stay in the bottle.
4. Take the syringe and check the plunger is fully down.
5. Keep the bottle upright and insert the oral syringe firmly into the plastic adaptor.
6. Turn the whole bottle with the syringe upside down.
7. Slowly pull the plunger down fully so that the syringe fills with medicine. Push the plunger back up completely to expel any large air bubbles that may be trapped inside the oral syringe.
8. Then pull the plunger slowly back to the volume you need for your dose.
9. Turn the whole bottle with the syringe the right way up and take the syringe out of the bottle.
10. The dose of medicine can now be swallowed directly from the oral syringe. Please ensure that you are sitting upright and the plunger must be pushed slowly to allow you to swallow the dose.
11. Replace the child resistant cap after use, leaving the adaptor in place.
12. Cleaning: After use, wipe the outside of the syringe with a dry, clean tissue.

Note: If necessary, Levothyroxine Oral Solution can be administered via a nasogastric feeding tube that should be rinsed twice with 10 ml of water immediately after administration.

If you take more Levothyroxine Oral Solution than you should

If you accidentally take an overdose of your medicine, either call your doctor straight away, or go to your nearest hospital casualty department. Symptoms of overdose

include fever, irregular heartbeat, muscle cramps, headache, restlessness, flushing, sweating or diarrhoea. Always take any remaining medicine, the container and the label with you, so that the medicine can be identified.

If you forget to take Levothyroxine Oral Solution

If you forget to take your medicine, take your dose when you remember and then take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose. If you have forgotten several doses tell your doctor when you have your next check-up or blood test.

If you stop taking Levothyroxine Oral Solution

It can be dangerous to stop taking your medicine without your doctor's advice.

If you are worried ask your doctor or pharmacist for advice.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. These usually happen if the dose you are taking is too high.

Tell your doctor if you have any of the following side effects while you are taking this medicine.

If any of the following happen, stop taking Levothyroxine Oral Solution and tell your doctor immediately or go to the casualty department at your nearest hospital

- swelling of the hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing
- hives
- fainting
- yellowing of the skin and eyes also called jaundice.

These are all very serious side effects. If you have them, you may have a serious allergic reaction to Levothyroxine Oral Solution. You may need urgent medical attention or hospitalisation. All of these very serious side effects are very rare.

Tell your doctor if you notice any of the following: Fast or irregular heartbeats, palpitations, chest pain, muscle cramps or weakness, headache, restlessness, excitability, flushing, sweating, diarrhoea, vomiting, fever, menstruation problems, tremor, sleeplessness, heat intolerance and excessive weight loss. Rash, itching and puffiness may also occur.

Very rarely, if far too much Levothyroxine Oral Solution has been taken in one go or over many years, the heart may fail and coma and death have been reported. If you feel unwell in any other way, tell your doctor as soon as you can.

Additional side effects in children

Children may have some hair loss at the beginning of treatment, however this is usually temporary and the hair returns.

Do not be alarmed by this list of possible events. You may not have any of them.

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

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme:

Website: www.yellowcard.mhra.gov.uk

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

5. How to store Levothyroxine Oral Solution

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

Do not store above 25˚C.

Store in the original package in order to protect from light.

Dispose of any remaining medicine 2 months after opening.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP (month, year). The expiry date refers to the last day of that month.

Levothyroxine Oral Solution is colourless and odourless. Do not use this medicine if you notice that the solution has a colour and/or an odour. Talk to your pharmacist.

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 protect the environment.

6. Contents of the pack and other information

What Levothyroxine Oral Solution contains

- The active substance is levothyroxine sodium. Each 5 ml of oral solution contains levothyroxine equivalent to levothyroxine sodium 25 micrograms, 50 micrograms, 100 micrograms or 125 micrograms.
- It also contains the following inactive ingredients: glycerol, citric acid anhydrous, sodium methyl parahydroxybenzoate (E219), citric acid 10% and purified water.

What Levothyroxine Oral Solution looks like and contents of the pack

Levothyroxine Oral Solution is a clear, colourless and odourless liquid. Each bottle contains 100ml of oral solution.

Levothyroxine Oral Solution is packed in an amber glass bottle, with a child-resistant, tamper-evident screw cap. A 5ml graduated oral dosing syringe and a "press-in" syringe/bottle adaptor are also provided.

Marketing Authorisation Holder

Creo Pharma Limited
Felsted Business Centre
Felsted
Essex
CM6 3LY
United Kingdom

Manufacturer

Quantum Pharmaceutical Limited
Quantum House
Hobson Industrial Estate
Hobson
Newcastle Upon Tyne
NE16 6EA
United Kingdom

This leaflet was last revised in November 2018

K0000

For use with question 55:

Equivalent doses of morphine sulfate and diamorphine hydrochloride given over 24 hours These equivalences are *approximate only* and should be adjusted according to response

ORAL MORPHINE	PARENTERAL MORPHINE	PARENTERAL DIAMORPHINE
Oral morphine sulfate **over 24 hours**	Subcutaneous infusion of morphine sulfate **over 24 hours**	Subcutaneous infusion of diamorphine hydrochloride **over 24 hours**
30 mg	15 mg	10 mg
60 mg	30 mg	20 mg
90 mg	45 mg	30 mg
120 mg	60 mg	40 mg
180 mg	90 mg	60 mg
240 mg	120 mg	80 mg
360 mg	180 mg	120 mg
480 mg	240 mg	160 mg
600 mg	300 mg	200 mg
780 mg	390 mg	260 mg
960 mg	480 mg	320 mg
1200 mg	600 mg	400 mg

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection equivalent to one-tenth to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle). To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.

For use with question 57+ 58, *please turn over*:

Heparin sodium 5,000 I.U./ml Solution for injection or concentrate for solution for infusion (without preservative)

Summary of Product Characteristics Updated 08-Oct-2018 | Wockhardt UK Ltd

1. Name of the medicinal product

Monoparin 5,000 I.U./ml Solution for injection or concentrate for solution for infusion or Heparin sodium 5,000 I.U./ml Solution for injection or concentrate for solution for infusion

2. Qualitative and quantitative composition

Heparin sodium 5,000 I.U./ml (5,000 I.U. in 1ml, 25,000 I.U. in 5ml)

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for injection or concentrate for solution for infusion

A colourless or straw-coloured liquid, free from turbidity and from matter that deposits on standing.

4. Clinical particulars

4.1 Therapeutic indications

Prophylaxis of deep vein thrombosis and pulmonary embolism

Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and acute peripheral arterial occlusion.

Prophylaxis of mural thrombosis following myocardial infarction.

In extracorporeal circulation and haemodialysis.

4.2 Posology and method of administration

Route of administration

By continuous intravenous infusion in 5% glucose or 0.9% sodium chloride or by intermittent intravenous injection, or by subcutaneous injection.

As the effects of heparin are short-lived, administration by intravenous infusion or subcutaneous injection is preferable to intermittent intravenous injections.

Recommended dosage

Prophylaxis of deep vein thrombosis and pulmonary embolism

Adults:

2 hours pre-operatively:	5,000 units subcutaneously
followed by:	5,000 units subcutaneously every 8-12 hours, for 7-10 days or until the patient is fully ambulant.

No laboratory monitoring should be necessary during low dose heparin prophylaxis. If monitoring is considered desirable, anti-Xa assays should be used as the activated partial thromboplastin time (APTT) is not significantly prolonged.

During pregnancy:	5,000 - 10,000 units every 12 hours, subcutaneously, adjusted according to APTT or anti-Xa assay.

Elderly:

Dosage reduction and monitoring of APTT may be advisable.

Children:

No dosage recommendations.

Treatment of deep vein thrombosis and pulmonary embolism:

Adults:

Loading dose:	5,000 units intravenously (10,000 units may be required in severe pulmonary embolism)
Maintenance:	1,000-2,000 units/hour by intravenous infusion,

or 10,000-20,000 units 12 hourly subcutaneously,
or 5,000-10,000 units 4-hourly by intravenous injection.

Elderly:

Dosage reduction may be advisable.

Children and small adults:

Loading dose:	50 units/kg intravenously
Maintenance:	15-25 units/kg/hour by intravenous infusion, or 250 units/kg 12 hourly subcutaneously or 100 units/kg 4-hourly by intravenous injection

Treatment of unstable angina pectoris and acute peripheral arterial occlusion:

Adults:

Loading dose:	5,000 units intravenously
Maintenance:	1,000-2,000 units/hour by intravenous infusion, or 5,000-10,000 units 4-hourly by intravenous injection.

Elderly:

Dosage reduction may be advisable.

Children and small adults:

Loading dose:	50 units/kg intravenously
Maintenance:	15-25 units/kg/hour by intravenous infusion, or 100 units/kg 4-hourly by intravenous injection

Daily laboratory monitoring (ideally at the same time each day, starting 4-6 hours after initiation of treatment) is essential during full-dose heparin treatment, with adjustment of dosage to maintain an APTT value 1.5-2.5 x midpoint of normal range or control value.

Prophylaxis of mural thrombosis following myocardial infarction

Adults:

12,500 units 12 hourly subcutaneously for at least 10 days.

Elderly:

Dosage reduction may be advisable

In extracorporeal circulation and haemodialysis

Adults:

Cardiopulmonary bypass:

Initially 300 units/kg intravenously, adjusted thereafter to maintain the activated clotting time (ACT) in the range 400-500 seconds.

Haemodialysis and haemofiltration:

Initially 1,000-5,000 units,

Maintenance: 1,000-2,000 units/hour, adjusted to maintain clotting time >40 minutes.

Heparin resistance

Patients with altered heparin responsiveness or heparin resistance may require disproportionately higher doses of heparin to achieve the desired effect. Also refer to section 4.4, Special warnings and precautions for use.

4.3 Contraindications

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

Heparin should not be administered by intramuscular injection or after major trauma.

Patients who consume large amounts of alcohol, who are sensitive to the drug, who are actively bleeding or who have haemophilia or other bleeding disorders, severe liver disease (including oesophageal varices), purpura, severe hypertension, active tuberculosis or increased capillary permeability.

Patients with present or previous thrombocytopenia. The rare occurrence of skin necrosis in patients receiving heparin contra-indicates the further use of heparin either by subcutaneous or intravenous routes because of the risk of thrombocytopenia.

Because of the special hazard of post-operative haemorrhage heparin is contra-indicated during surgery of the brain, spinal cord and eye, in procedures at sites where there is a risk of bleeding, in patients that have had recent surgery, and in patients undergoing lumbar puncture or regional anaesthetic block.

The relative risks and benefits of heparin should be carefully assessed in patients with a bleeding tendency or those patients with an actual or potential bleeding site eg. hiatus hernia, peptic ulcer, neoplasm, bacterial endocarditis, retinopathy, bleeding haemorrhoids, suspected intracranial haemorrhage, cerebral thrombosis or threatened abortion.

In patients receiving heparin for treatment rather than prophylaxis, locoregional anaesthesia in elective surgical procedures is contraindicated because use of heparin may be very rarely associated with epidural or spinal haematoma resulting in prolonged or permanent paralysis. If such a procedure is planned the heparin should be stopped and the procedure should be delayed until the aPTT has returned to normal. Epidural anaesthesia use during birth in pregnant women treated with heparin is contraindicated (see section 4.6).

Menstruation is not a contra-indication.

Concomitant use of intravenous diclofenac with heparin (including low dose heparin) is contraindicated.

4.4 Special warnings and precautions for use

Platelet counts should be measured in patients receiving heparin treatment for longer than 5 days and the treatment should be stopped immediately in those who develop thrombocytopenia.

Heparin induced thrombocytopenia (HIT) and heparin induced thrombocytopenia with thrombosis (HITT) can occur up to several weeks after discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT or HITT.

In patients with advanced renal or hepatic disease, a reduction in dosage may be necessary. The risk of bleeding is increased with severe renal impairment and in the elderly (particularly elderly women).

Although heparin hypersensitivity is rare, it is advisable to give a trial dose of 1,000 I.U. in patients with a history of allergy. Caution should be exercised in patients with known hypersensitivity to low molecular weight heparins.

In most patients, the recommended low-dose regimen produces no alteration in clotting time. However, patients show an individual response to heparin, and it is therefore essential that the effect of therapy on coagulation time should be monitored in patients undergoing major surgery.

Caution is recommended in patients receiving heparin prophylactically and undergoing spinal or epidural anaesthesia or spinal puncture (risk of spinal or epidural haematoma resulting in prolonged or permanent paralysis). The risk is increased by the use of a peridural or spinal catheter for anaesthesia, by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or anticoagulants and by traumatic or repeated puncture.

In decision making on the interval between the last administration of heparin at prophylactic doses and the placement or removal of a peridural or spinal catheter, the product characteristics and the patient profile should be taken into account. Subsequent dose should not take place before at least four hours have elapsed. Re-administration should be delayed until the surgical procedure is completed.

Should a physician decide to administer anticoagulation in the context of peridural or spinal anaesthesia, extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment, such as back pain, sensory and motor deficits and bowel or bladder dysfunction. Patients should be instructed to inform a nurse or clinician immediately if they experience any of these.

Heparin can suppress adrenal secretion of aldosterone leading to hyperkalemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium, or taking potassium sparing drugs. The risk of hyperkalemia appears to increase with duration of therapy but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin therapy and in all patients treated for more than 7 days.

Heparin resistance

There is considerable variation in individual anticoagulant responses to heparin.

Heparin resistance, defined as an inadequate response to heparin at a standard dose for achieving a therapeutic goal occurs in approximately 5 to 30% of patients.

Factors predisposing to the development of heparin resistance, include:

• Antithrombin III activity less than 60% of normal (antithrombin III-dependent heparin resistance):

Reduced antithrombin III activity may be hereditary or more commonly, acquired (secondary to preoperative heparin therapy in the main, chronic liver disease, nephrotic syndrome, cardiopulmonary bypass, low grade disseminated intravascular coagulation or drug induced, e.g. by aprotinin, oestrogen or possibly nitroglycerin)

• Patients with normal or supranormal antithrombin III levels (antithrombin III-independent heparin resistance)

- Thromboembolic disorders
- Increased heparin clearance

• Elevated levels of heparin binding proteins, factor VIII, von Willebrand factor, fibrinogen, platelet factor 4 or histidine-rich glycoprotein

- Active infection (sepsis or endocarditis)
- Preoperative intra-aortic balloon counterpulsation
- Thrombocytopenia
- Thrombocytosis
- Advanced age
- Plasma albumin concentration ≤ 35g/dl
- Relative hypovolaemia

Heparin resistance is also often encountered in acutely ill patients, in patients with malignancy and during pregnancy or the post-partum period.

Drugs affecting platelet function or the coagulation system should in general not be given concomitantly with heparin (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Analgesics: Drugs that interfere with platelet aggregation eg. aspirin and other NSAIDs should be used with care. Increased risk of haemorrhage with;

- ketorolac

- intravenous diclofenac (refer to section 4.3)

Avoid concomitant use of either ketorolac or intravenous diclofenac, even with low – dose heparin.

Anticoagulants, platelet inhibitors, etc: Increased risk of bleeding with oral anticoagulants, epoprostenol, clopidogrel, ticlopidine, streptokinase, dipyridamole, dextran solutions, abciximab, eptifibatide or any other drug which may interfere with coagulation.

Cephalosporins: Some cephalosporins, e.g. cefaclor, cefixime and ceftriaxone, can affect the coagulation process and may therefore increase the risk of haemorrhage when used concurrently with heparin.

ACE inhibitors, angiotensin-II receptor antagonists or the renin inhibitor aliskiren: Hyperkalaemia may occur with concomitant use.

Nitrates: Reduced activity of heparin has been reported with simultaneous intravenous glyceryl trinitrate infusion.

Probenecid: May increase the anticoagulant effects of heparin.

Tobacco smoke: Nicotine may partially counteract the anticoagulant effect of heparin. Increased heparin dosage may be required in smokers.

Interference with diagnostic tests may be associated with pseudo-hypocalcaemia (in haemodialysis patients), artefactual increases in total thyroxine and triiodothyronine, simulated metabolic acidosis and inhibition of the chromogenic lysate assay for endotoxin. Heparin may interfere with the determination of aminoglycosides by immunoassays.

4.6 Fertility, pregnancy and lactation

Heparin is not contraindicated in pregnancy. Heparin does not cross the placenta or appear in breast milk. The decision to use heparin in pregnancy should be taken after evaluation of the risk/benefit in any particular circumstances.

Osteoporosis has been reported with prolonged heparin treatment during pregnancy.

Particular caution is required at the time of delivery. Due to the risk of uteroplacental haemorrhage, heparin treatment should be stopped at the onset of labour.

If epidural anaesthesia is envisaged, heparin treatment should be suspended whenever possible.

Use in women with threatened abortion is contraindicated (refer to section 4.3).

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

Blood disorders:

Haemorrhage (see also Special Warnings and Precautions and Overdosage Information).

Thrombocytopenia has been observed occasionally (see also Special Precautions and Warnings). It has been reported that thrombocytopenia occurs more frequently with bovine-derived heparin than porcine-derived heparin. Two types of heparin-induced thrombocytopenia have been defined. Type I is frequent, mild (usually >50 x 10^9/L) and transient, occurring within 1-5 days of heparin administration. Type II is less frequent but often associated with severe thrombocytopenia (usually <50 x 10^9/L). It is immune-mediated and occurs after a week or more (earlier in patients previously exposed to heparin). It is associated with the production of a platelet-aggregating antibody and thromboembolic complications, due to platelet-rich thrombi (the 'white clot syndrome'), which may precede the onset of thrombocytopenia. Pulmonary embolism has been reported as thromboembolic complications of heparin-induced thrombocytopenia. Heparin should be discontinued immediately in patients who develop thrombocytopenia.

Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis (HITT) can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT and HITT.

Endocrine disorders:

Adrenal insufficiency secondary to adrenal haemorrhage has been associated with heparin (rarely). Heparin products can cause hypoaldosteronism which may result in an increase in plasma potassium. Rarely, clinically significant hyperkalemia may occur particularly in patients with chronic renal failure and diabetes mellitus (see Warnings and Precautions).

Hepatic disorders:

Increased serum transaminase values may occur but usually resolve on discontinuation of heparin.

Immune system disorders:

Hypersensitivity reactions to heparin are rare. They include urticaria, conjunctivitis, rhinitis, asthma, cyanosis, tachypnoea, feeling of oppression, fever, chills, angioneurotic oedema and anaphylactic shock.

Metabolic disorders:

Heparin administration is associated with release of lipoprotein lipase into the plasma; rebound hyperlipidaemia may follow heparin withdrawal.

Muscle and tissue disorders:

There is some evidence that prolonged dosing with heparin (i.e. over many months) may cause osteoporosis and fractures in the vertebra and ribs. Significant bone demineralisation has been reported in women taking more than 10,000 I.U. per day of heparin for three months or longer.

Reproductive and breast disorders:

Priapism has been reported.

Skin and subcutaneous tissue disorders:

Local irritation and skin necrosis may occur but are rare. There is some evidence that prolonged dosing with heparin (i.e. over many months) may cause alopecia.

Erythematous nodules, or infiltrated and sometimes eczema-like plaques, at the site of subcutaneous injections are common, occurring 3-21 days after starting heparin treatment.

Pruritus

Rash (including erythematous and maculopapular)

Vascular disorders:

Haematoma. Very rare cases of epidural and spinal haematoma have been reported in patients receiving heparin for prophylaxis undergoing spinal or epidural anaesthesia or spinal puncture.

Reporting of suspected adverse reactions

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

4.9 Overdose

A potential hazard of heparin therapy is haemorrhage, but this is usually due to overdosage and the risk is minimised by strict laboratory control. Slight haemorrhage can usually be treated by withdrawing the drug. If bleeding is more severe, clotting time and platelet count should be determined. Prolonged clotting time will indicate the presence of an excessive anticoagulant effect requiring neutralisation by intravenous protamine sulfate, at a dosage of 1 mg for every 100 I.U. of heparin to be neutralised. The bolus dose of protamine sulfate should be given slowly over about 10 minutes and not

For use with question 59:

R. Damon, MRCVS
We Love Animals Surgery
7 Care Lane,
W1 1JB
Tel: 02085750005

Furry the Cat
Owned by Mrs R, 70 Care Lane, W1 1JB

Supply Flucloxacillin 500mg capsules. Give as directed x 28 capsules

Prescribed under the veterinary cascade.

28/11/2020

NICE National Institute for Health and Care Excellence

MEFLOQUINE

Indications and dose

Treatment of malaria

By mouth

For Adult
(consult product literature).

Prophylaxis of malaria

By mouth

For Child (body-weight 5–15 kg)
62.5 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.

For Child (body-weight 16–24 kg)
125 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.

For Child (body-weight 25–44 kg)
187.5 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.

For Child (body-weight 45 kg and above)
250 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.

For Adult (body-weight 45 kg and above)
250 mg once weekly, dose to be started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving.

Unlicensed use

Mefloquine doses in BNF Publications may differ from those in product literature.

In children

Not licensed for use in children under 5 kg body-weight and under 3 months.

Contra-indications

Avoid for prophylaxis if history of psychiatric disorders (including depression) or convulsions; avoid for standby treatment if history of convulsions; history of blackwater fever

Cautions

Cardiac conduction disorders; epilepsy (avoid for prophylaxis); not recommended in infants under 3 months (5 kg) (in children); traumatic brain injury

Cautions, further information

Neuropsychiatric reactions

Mefloquine is associated with potentially serious neuropsychiatric reactions. Abnormal dreams, insomnia, anxiety, and depression occur commonly. Psychosis, suicidal ideation, and suicide have also been reported. Psychiatric symptoms such as insomnia, nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodromal for a more serious event. Adverse reactions may occur and persist up to several months after discontinuation because mefloquine has a long half-life. For a prescribing checklist, and further information on side-effects, particularly neuropsychiatric side-effects, which may be associated with the use of mefloquine for malaria prophylaxis, see the *Guide for Healthcare Professionals* provided by the manufacturer.

Interactions

Individual interactants:

- Mefloquine (/interaction/mefloquine-2.html)

Side-effects

Common or very common

Anxiety; depression; diarrhoea; dizziness; gastrointestinal discomfort; headache; nausea; skin reactions; sleep disorders; vision disorders; vomiting

Frequency not known

Acute kidney injury; agranulocytosis; alopecia; aplastic anaemia; appetite decreased; arrhythmias; arthralgia; asthenia; behaviour abnormal; cardiac conduction disorders; cataract; chest pain; chills; concentration impaired; confusion; cranial nerve paralysis; delusional disorder; depersonalisation; drowsiness; dyspnoea; encephalopathy; eye disorder; fever; flushing; gait abnormal; hallucination; hearing impairment; hepatic disorders; hyperacusia; hyperhidrosis; hypertension; hypotension; leucocytosis; leucopenia; malaise; memory loss; mood altered; movement disorders; muscle complaints; muscle weakness; nephritis; nerve disorders; oedema; palpitations; pancreatitis; paraesthesia; pneumonia; pneumonitis; psychosis; seizure; self-endangering behaviour; speech disorder; Stevens-Johnson syndrome; suicidal tendencies; syncope; thrombocytopenia; tinnitus; tremor; vertigo

Allergy and cross-sensitivity

Contra-indications

Contra-indicated in patients with hypersensitivity to quinine.

Conception and contraception

Manufacturer advises adequate contraception during prophylaxis and for 3 months after stopping (teratogenicity in *animal* studies).

Pregnancy

Manufacturer advises avoid (particularly in the first trimester) unless the potential benefit outweighs the risk; however, studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas.

Breast feeding

Present in milk but risk to infant minimal.

Hepatic impairment

Manufacturer advises avoid in severe impairment—elimination may be prolonged.

Renal impairment

Manufacturer advises caution.

Directions for administration

Tablet may be crushed and mixed with food such as jam or honey just before administration

Patient and carer advice

Manufacturer advises that patients receiving mefloquine for malaria prophylaxis should be informed to discontinue its use if neuropsychiatric symptoms occur and seek immediate medical advice so that mefloquine can be replaced with an alternative antimalarial. Travellers should also be warned about **importance** of avoiding mosquito bites, **importance** of taking prophylaxis regularly, and **importance** of immediate visit to doctor if ill within 1 year and especially within 3 months of return.

Patient resources

A patient alert card should be provided.

Driving and skilled tasks

Dizziness or a disturbed sense of balance may affect performance of skilled tasks (e.g. driving); effects may occur and persist up to several months after stopping mefloquine.

National funding/access decisions

NHS restrictions

Drugs for malaria prophylaxis are not prescribable in NHS primary care; health authorities may investigate circumstances under which antimalarials are prescribed.

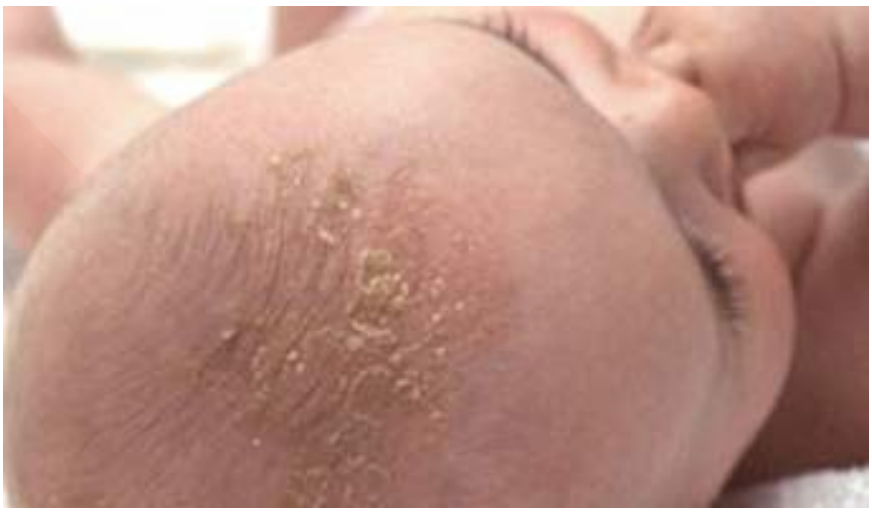
Medicinal forms

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

Tablet (../medicinal-forms/mefloquine.html)

For use with question 72:

-



Aciclovir Tablets BP 800mg

Summary of Product Characteristics Updated 12-Sep-2018 | Accord-UK Ltd

1. Name of the medicinal product

ACICLOVIR TABLETS BP 800mg

2. Qualitative and quantitative composition

Each tablet contains 800mg Aciclovir PhEur.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

White uncoated tablets.

4. Clinical particulars

4.1 Therapeutic indications

1) Treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

4.2 Posology and method of administration

Posology

***Adults: Treatment of herpes zoster infections*:** 800mg aciclovir should be taken five times daily at approximately four-hourly intervals, omitting the night time dose. Treatment should continue for seven days.

In severely immunocompromised patients (*eg* after marrow transplant) or in patients with impaired absorption from the gut, consideration should be given to intravenous dosing.

Dosing should begin as early as possible after the start of an infection. Treatment of herpes zoster yields better results if initiated as soon as possible after the onset of the rash.

Dosage in the paediatric population: Treatment of varicella infection: Children aged 6 years and over should be given 800mg four times daily. Treatment should continue for 5 days. Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg four times daily).

No specific data are available on the *suppression of herpes simplex* infections or the *treatment of herpes zoster* infections in immunocompetent children. When treatment of herpes zoster infections is required in immunocompromised children, intravenous dosing should be considered.

***Dosage in the elderly*:** The possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly (see Dosage in renal impairment below).

In the elderly, total aciclovir body clearance declines along with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

***Dosage in renal impairment*:** Caution is advised when administering aciclovir to patients with impaired renal function. Adequate hydration should be maintained.

In the management of herpes simplex infections in patients with severe renal impairment (creatinine clearance less than 10 ml/minute) an adjustment of dosage to 200 mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.

In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800mg aciclovir twice daily at approximately twelve-hourly intervals for patients with severe renal impairment (creatinine clearance less than 10ml/minute), and to 800mg aciclovir three times daily at intervals of approximately six to eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25ml/minute).

In the treatment of herpes zoster infections it is recommended to adjust the dosage to 800mg aciclovir twice daily at approximately twelve-hourly intervals for patients with renal impairment (creatinine clearance less than 10ml/minute), and to 800mg aciclovir three times daily at intervals of approximately six to eight hours for patients with moderate renal impairment (creatinine clearance in the range 10-25ml/minute).

Method of Administration

Administration: Patients who experience difficulty in swallowing the tablets may disperse them in a minimum of 50ml water which should be stirred before drinking.

For oral administration.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Use in patients with renal impairment and in elderly patients:

The risk of renal impairment is increased by use with other nephrotoxic drugs.

Aciclovir is eliminated by renal clearance, therefore the dose must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Prolonged or repeated courses of aciclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment (see section 5.1).

Hydration status: Care should be taken to maintain adequate hydration in patients receiving higher dose oral regimens or i.v., e.g. for the treatment of herpes zoster infection (4g daily), in order to avoid the risk of possible renal toxicity.

4.5 Interaction with other medicinal products and other forms of interaction

• Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any drugs administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations.

• Ciclosporin: There has been a small number of transplant patients with increased serum levels of ciclosporin and signs of nephrotoxicity when aciclovir is given concurrently. Renal function should be monitored closely in patients taking both drugs.

• Cimetidine and probenecid: Cimetidine and probenecid increase the AUC of aciclovir by competing for active secretion by the renal tubules and reduce aciclovir renal clearance. Dosage adjustment is usually not necessary because of the wide therapeutic index of aciclovir.

• Mycophenolate mofetil: Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when the drugs are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

• An experimental study on five male subjects indicates that concomitant therapy with aciclovir increases AUC of totally administered theophylline with approximately 50%. It is recommended to measure plasma concentrations during concomitant therapy with aciclovir.

• Zidovudine: Although co-administration of zidovudine and aciclovir is not usually associated with toxicity, there is a single case report of overwhelming fatigue developing in a patient when given the two drugs together. This did not occur when zidovudine and aciclovir were given alone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Experience in humans is limited so the use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. Herpes simplex encephalitis and varicella pneumonia constitute a significant risk for mother and foetus and primary genital herpes may retard intrauterine growth and increase the risk of premature birth and neonatal herpes infection. (See section 5.3 Preclinical Safety Data). Aciclovir readily crosses the placenta and levels in cord blood are higher than in maternal serum.

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects amongst aciclovir exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats or mice. In a non-standard test in rats, foetal abnormalities were observed but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Breast-Feeding

Following oral administration of 200mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6-4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing mother.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of aciclovir should be borne in mind when considering the patients's ability to drive or operate machinery.

As aciclovir administration is occasionally associated with drowsiness and somnolence (usually in patients receiving high doses or with impaired renal function), patients should make sure that they are not affected before driving or using machinery.

There have been no studies to investigate the effect of aciclovir on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

An estimate of the frequency of undesirable effects has been included though this is not certain for all adverse effects. The following convention has been used for the classification of undesirable effects in terms of frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000, very rare (<1/10000).

Blood and the lymphatic system disorders

Very rare: Anaemia, leucopenia and thrombocytopenia.

Immune system disorders

Rare: Anaphylaxis.

Nervous system disorders

Common: Dizziness and headache.

Very rare: Reversible neurological reactions including agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, drowsiness, confusional states, hallucinations, somnolence, convulsions, coma and malaise. These effects were usually reported in patients receiving high doses of aciclovir (usually given intravenously), with renal impairment, or with other predisposing factors (see section 4.4). Aciclovir should be used with caution in patients with underlying neurological abnormalities.

Respiratory, thoracic and mediastinal disorders

Rare: Dyspnoea

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea and abdominal pain.

Hepato-biliary disorders

Rare: Reversible rises in bilirubin and liver related enzymes.

Very rare: Hepatitis and jaundice.

Skin and sub-cutaneous tissue disorders

Common: Skin rashes, pruritus (including photosensitivity).

Uncommon: Urticaria, accelerated diffuse hair loss .

Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.*Rare:* Angioedema, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis.

Renal and urinary disorders

Rare: Increases in blood urea and creatinine; renal impairment, usually during intravenous therapy, which is usually reversible and responds to hydration and/or dosage reduction but may progress to acute renal failure in patients with predisposing factors.

Very rare: Acute renal failure, renal pain

Renal pain may be associated with renal failure.

General disorders

Common: Fatigue, fever.

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms and signs

Aciclovir is only partly absorbed in the gastrointestinal tract.

Patients have ingested overdoses of up to 20 g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (*eg* nausea and vomiting) and neurological effects (*eg* headache and confusion).

Overdosage of i.v. aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group - ATC code: J05A B

Aciclovir is an antiviral agent which is highly active *in vitro* against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependant on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting the normal cellular processes.

Herpes simplex virus develops resistance to aciclovir by selection of mutants deficient in thymidine kinase which are usually of diminished virulence with reduced infectivity and latency. Resistance is rare in immunocompetent patients on short courses of oral therapy but it is more prevalent in immunocompromised patients who have often received prolonged courses of treatment. Herpes zoster resistance develops by a similar mechanism and has been reported in immunocompromised patients undergoing prolonged therapy with aciclovir.

5.2 Pharmacokinetic properties

Absorption

Aciclovir is slowly and incompletely absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 2 hours following ingestion.

Distribution

There is a wide distribution to various tissues, including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9-33%. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately 3 times higher than those in maternal serum.

Metabolism and Elimination

Renal excretion is the major route of elimination by both glomerular filtration and tubular secretion. The terminal or beta-phase half-life is reported to be about 2-3 hours for adults without renal impairment. As aciclovir persists in the plasma of patients with renal insufficiency, in chronic renal failure this value is increased and may be up to 19.5 hours in anuric patients. As renal function decreases, a greater percentage of the drug is eliminated by metabolic conversion to carboxymethoxymethyl guanine. During haemodialysis the half-life is reduced to 5.7 hours, with 60% of a dose of aciclovir being removed in 6 hours. Faecal excretion may account for about 2% of a dose.

In neonates and young infants (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the Cssmax was found to be 61.2 microMol (13.8 micrograms/ml) and Cssmin to be 10.1 microMol (2.3 micrograms/ml). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 microgram/ml) and Cmin of 14.1 micromolar (3.2 microgram/ml).

5.3 Preclinical safety data

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice. In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Two generation studies in mice do not reveal any effect of aciclovir on fertility.

The results of a wide range of mutagenicity tests *in vitro* and *in vivo* indicate that aciclovir does not pose a genetic risk to man. Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse. Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Aciclovir has been shown to have no definite effect upon sperm count, morphology or motility in man.

For use with question 79:

Pharmacy stamp *Please don't stamp over age box*	Age D.O.B 8/9/1962	Title, Forename, Surname & Address Miss G 47-49 Park Royal Road London, NW10 7LQ
Number of day's treatment		NHS Number
Endorsements	Sodium valproate 500mg tablets Take one tablet twice a day Supply 112 tablets	
Signature of Prescriber		Date 15/12/2020
For Dispenser No. Of Prescns. on form	Dr Amazing 1234567 The Best Surgery 700 Lovely Street, WC1 1JN FP10	

Sinemet CR 50 mg/200 mg Prolonged-Release Tablets

Summary of Product Characteristics Updated 25-Oct-2017 | Merck Sharp & Dohme Limited

1. Name of the medicinal product

SINEMET® CR 50 mg/200 mg Prolonged-Release Tablets

HALF SINEMET® CR 25 mg/100 mg Prolonged-Release Tablets

2. Qualitative and quantitative composition

Each tablet of 'Sinemet CR' contains carbidopa (equivalent to 50 mg of anhydrous carbidopa) and 200 mg levodopa.

Each tablet of 'Half Sinemet CR' contains carbidopa (equivalent to 25 mg of anhydrous carbidopa) and 100 mg levodopa.

3. Pharmaceutical form

Modified-release tablets.

'Sinemet CR': peach-coloured, oval shaped, biconvex tablets, one side deep-scored and the other marked '521'.

'Half Sinemet CR': pink-coloured, oval-shaped, biconvex tablets, plain one side and the other marked '601'.

4. Clinical particulars

4.1 Therapeutic indications

Antiparkinson agent.

Idiopathic Parkinson's disease, in particular to reduce off-period in patients who previously have been treated with levodopa/decarboxylase inhibitors, or with levodopa alone and who have experienced motor fluctuations. The experience is limited with 'Sinemet CR' and 'Half Sinemet CR' in patients who have not been treated with levodopa before.

4.2 Posology and method of administration

'Sinemet CR' and 'Half Sinemet CR' tablets contain a 1:4 ratio of carbidopa to levodopa ('Sinemet CR': carbidopa 50 mg/levodopa 200 mg, 'Half Sinemet CR' 25 mg/100 mg per tablet). The daily dosage of 'Sinemet CR' must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of nausea or abnormal involuntary movements, including dyskinesias, chorea and dystonia.

Route of administration: oral

'Sinemet CR' and 'Half Sinemet CR' may only be administered as whole tablets. So that the controlled release properties of the product can be maintained, tablets should not be chewed, crushed, or halved.

Standard antiparkinson drugs, other than levodopa alone, may be continued while 'Sinemet CR' or 'Half Sinemet CR' are being administered, although their dosage may have to be adjusted. Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, 'Sinemet CR' or 'Half Sinemet CR' can be given to patients receiving supplemental pyridoxine (vitamin B6).

Initial Dose

Patients currently treated with conventional levodopa/decarboxylase inhibitor combinations

Dosage with 'Sinemet CR' should be substituted initially at an amount that provides no more than approximately 10% more levodopa per day when higher dosages are given (more than 900 mg per day). The dosing interval between doses should be prolonged by 30 to 50% at intervals ranging from 4 to 12 hours. It is recommended to give the smaller dose, if divided doses are not equal, at the end of the day. The dose needs to be titrated further depending on clinical response, as indicated below under 'Titration'. Dosages that provide up to 30% more levodopa per day may be necessary.

A guide for substitution of 'Sinemet CR' treatment for conventional levodopa/decarboxylase inhibitor combinations is shown in the table below:

Guideline for Conversion from 'Sinemet' to 'Sinemet CR'

'Sinemet'	**'Sinemet CR'**	
Daily Dosage	Daily Dosage	
Levodopa (mg)	Levodopa (mg)	Dosage Regimen
300 - 400	400	1 Tablet 2 x daily
500 - 600	600	1 Tablet 3 x daily
700 - 800	800	4 Tablets in 3 or more divide doses

900 - 1000	1000	5 Tablets in 3 or more divided doses
1100 - 1200	1200	6 Tablets in 3 or more divided doses
1300 - 1400	1400	7 Tablets in 3 or more divided doses
1500 - 1600	1600	8 Tablets in 3 or more divided doses

'Half Sinemet CR' is available to facilitate titration when 100 mg steps are required.

Patients currently treated with levodopa alone

Levodopa must be discontinued at least eight hours before therapy with 'Sinemet CR' is started. In patients with mild to moderate disease, the initial recommended dose is one tablet of 'Sinemet CR' twice daily.

Patients not receiving levodopa

In patients with mild to moderate disease, the initial recommended dose is one tablet of 'Sinemet CR' twice daily. Initial dosages should not exceed 600 mg per day of levodopa, nor be given at intervals of less than six hours.

Titration

Following initiation of therapy, doses and dosing intervals may be increased or decreased, depending upon therapeutic response. Most patients have been adequately treated with two to eight tablets per day of 'Sinemet CR' administered as divided doses at intervals ranging from four to twelve hours during the waking day. Higher doses (up to 12 tablets) and shorter intervals (less than four hours) have been used, but are not usually recommended.

When doses of 'Sinemet CR' are given at intervals of less than four hours, or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day. In some patients the onset of effect of the first morning dose may be delayed for up to one hour compared with the response usually obtained from the first morning dose of 'Sinemet'.

An interval of at least three days between dosage adjustments is recommended.

Maintenance

Because Parkinson's disease is progressive, periodic clinical evaluations are recommended and adjustment of the dosage regimen of 'Sinemet CR' or 'Half Sinemet CR' may be required.

Addition of other antiparkinson medication

Anticholinergic agents, dopamine agonists and amantadine can be given with 'Sinemet CR' or 'Half Sinemet CR'. Dosage adjustment of 'Sinemet CR' or 'Half Sinemet CR' may be necessary when these agents are added to an existing treatment regimen for 'Sinemet CR' or 'Half Sinemet CR'.

Interruption of therapy

Patients should be observed carefully if abrupt reduction or discontinuation of 'Sinemet CR' or 'Half Sinemet CR' is required, especially if the patient is receiving antipsychotics (see 4.4 'Special warnings and precautions for use').

Use in Children

Safety and effectiveness of 'Sinemet CR' or 'Half Sinemet CR' in infants and children have not been established, and its use in patients below the age of 18 is not recommended.

4.3 Contraindications

'Sinemet CR' or 'Half Sinemet CR' should not be given when administration of a sympathomimetic amine is contraindicated.

Non-selective monoamine oxidase (MAO) inhibitors are contraindicated for use with 'Sinemet CR' or 'Half Sinemet CR'. These inhibitors must be discontinued at least two weeks prior to initiating therapy with 'Sinemet CR' or 'Half Sinemet CR'. 'Sinemet CR' or 'Half Sinemet CR' may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g. selegiline hydrochloride) (See 4.5 'Interactions with other medicinal products and other forms of interaction').

'Sinemet CR' or 'Half Sinemet CR' is contraindicated in patients with known hypersensitivity to any component of this medication, and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, 'Sinemet CR' or 'Half Sinemet CR' should not be used in patients with suspicious undiagnosed skin lesions or a history of melanoma.

Use in patients with severe psychoses.

4.4 Special warnings and precautions for use

When patients are receiving levodopa monotherapy, levodopa must be discontinued at least eight hours before therapy with 'Sinemet CR' or 'Half Sinemet CR' is started (at least 12 hours if slow-release levodopa has been administered).

Dyskinesias may occur in patients previously treated with levodopa alone because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed. The occurrence of dyskinesias may require dosage reduction.

'Sinemet CR' and 'Half Sinemet CR' are not recommended for the treatment of drug-induced extrapyramidal reactions or for the treatment of Huntingdon's chorea.

Based on the pharmacokinetic profile of 'Sinemet CR' the onset of effect in patients with early morning dyskinesias may be slower than with conventional 'Sinemet'. The incidence of dyskinesias is slightly higher during treatment with 'Sinemet CR' than with conventional 'Sinemet' (16.5% vs 12.2%) in advanced patients with motor fluctuations.

'Sinemet CR' or 'Half Sinemet CR' should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease, or with a history of peptic ulcer disease or of convulsions.

Care should be exercised in administering 'Sinemet CR' or 'Half Sinemet CR' to patients with a history of recent myocardial infarction who have residual atrial, nodal, or ventricular arrhythmia. In such patients, cardiac function should be monitored with particular care during the period of initial dosage administration and titration.

Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

As with levodopa, 'Sinemet CR' or 'Half Sinemet CR' may cause involuntary movements and mental disturbances. Patients with a history of severe involuntary movements or psychotic episodes when treated with levodopa alone or levodopa/decarboxylase inhibitor combination should be observed carefully when 'Sinemet CR' or 'Half Sinemet CR' is substituted. These reactions are thought to be due to increased brain dopamine following administration of levodopa and use of 'Sinemet CR' or 'Half Sinemet CR' may cause recurrence. Dosage reduction may be required. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of carbidopa-levodopa combinations is reduced abruptly or discontinued, especially if the patient is receiving antipsychotics.

Patients with chronic wide-angle glaucoma may be treated cautiously with 'Sinemet CR' or 'Half Sinemet CR', provided the intraocular pressure is well controlled and the patient monitored carefully for changes in intraocular pressure during therapy.

Periodic evaluations of hepatic, haematopoietic, cardiovascular and renal function are recommended during extended therapy.

If general anaesthesia is required, 'Sinemet CR' or 'Half Sinemet CR' may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medicine.

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population (approximately 2-6 fold higher). It is unclear whether the increased risk observed was due to Parkinson's disease, or other factors such as drugs used to treat Parkinson's disease. Therefore patients and providers are advised to monitor for melanomas on a regular basis when using 'Sinemet CR' for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Laboratory Tests

Abnormalities in various laboratory tests have occurred with carbidopa-levodopa preparations and may occur with 'Sinemet CR' or 'Half Sinemet CR'. These include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), LDH, bilirubin, blood urea nitrogen, creatinine, uric acid and positive Coombs' test.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glycosuria.

Decreased haemoglobin and haematocrit, elevated serum glucose and white blood cells, bacteria and blood in the urine have been reported with standard 'Sinemet'.

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with carbidopa/ levodopa. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS (see also section 4.8).

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Sinemet. Review of treatment is recommended if such symptoms develop.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when the following drugs are administered concomitantly with 'Sinemet CR' or 'Half Sinemet CR':

Antihypertensive agents

Symptomatic postural hypotension has occurred when levodopa/decarboxylase inhibitor combinations were added to the treatment of patients receiving some antihypertensive drugs. Therefore when therapy with 'Sinemet CR' or 'Half Sinemet CR' is started, dosage adjustment of the antihypertensive drug may be required.

Antidepressants

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations. (For patients receiving monamine oxidase inhibitors, see 4.3 'Contraindications').

Anticholinergics

Anticholinergics may affect the absorption and thus the patient's response.

Iron

Studies demonstrate a decrease in the bioavailability of carbidopa and/or levodopa when it is ingested with ferrous sulphate or ferrous gluconate.

Other drugs

Dopamine D2 receptor antagonists (e.g. phenothiazines, butyrophenones and risperidone) and isoniazid may reduce the therapeutic effects of levodopa. The beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with 'Sinemet CR' or 'Half Sinemet CR' should be observed carefully for loss of therapeutic response.

Use of 'Sinemet CR' with dopamine-depleting agents (e.g., tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.

Concomitant therapy with selegiline and carbidopa-levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa-levodopa alone (See 4.3 'Contraindications').

Since levodopa competes with certain amino acids, the absorption of levodopa may be impaired in some patients on a high protein diet.

The effect of simultaneous administration of antacids with 'Sinemet CR' or 'Half Sinemet CR' on the bioavailability of levodopa has not been studied.

4.6 Pregnancy and lactation

There are insufficient data to evaluate the possible harmfulness of this substance when used in human pregnancy (See 5.3 'Preclinical Safety Data'). It is not known whether carbidopa is excreted in human milk. In a study of one nursing mother with Parkinson's disease, excretion of levodopa in breast milk was reported. 'Sinemet CR' or 'Half Sinemet CR' should not be given during pregnancy and to nursing mothers.

4.7 Effects on ability to drive and use machines

Individual responses to medication may vary. Certain side effects that have been reported with 'Sinemet CR' may affect some patients' ability to drive or operate machinery. Patients treated with levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or other at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section 4.4 'Special warnings and precautions for use').

4.8 Undesirable effects

In controlled clinical trials in patients with moderate to severe motor fluctuations 'Sinemet CR' did not produce side-effects which were unique to the modified-release formulation.

The side-effect reported most frequently was dyskinesia (a form of abnormal involuntary movements). A greater incidence of dyskinesias was seen with 'Sinemet CR' than with 'Sinemet'.

Other side-effects that also were reported frequently (above 2%) were: nausea, hallucinations, confusion, dizziness, chorea and dry mouth.

Side effects occurring less frequently (1-2%) were: dream abnormalities, dystonia, somnolence, insomnia, depression, asthenia, vomiting and anorexia.

Other side effects reported in clinical trials or in post-marketing experience include:

Body as a whole: chest pain, syncope.

Cardiovascular: palpitation, orthostatic effects including hypotensive episodes.

Gastro-intestinal: constipation, diarrhoea, dyspepsia, gastro-intestinal pain, dark saliva.

Hypersensitivity: angioedema, urticaria, pruritus.

Metabolic: weight loss.

Nervous System/Psychiatric: neuroleptic malignant syndrome (see 4.3 'Contraindications'), agitation, anxiety, decreased mental acuity, paraesthesia, disorientation, fatigue, headache, extrapyramidal and movement disorders, falling, gait abnormalities, muscle cramps, on-off phenomenon, increased libido, psychotic episodes including delusions and paranoid ideation. Levodopa is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Respiratory: dyspnoea

Skin: flushing, alopecia, rash, dark sweat.

Special Senses: blurred vision.

Urogenital: dark urine.

Other side effects that have been reported with levodopa or levodopa/carbidopa combinations and may be potential side-effects with 'Sinemet CR' are listed below:

Cardiovascular: cardiac irregularities, hypertension, phlebitis.

Gastro-intestinal: bitter taste, sialorrhoea, dysphagia, bruxism, hiccups, gastro-intestinal bleeding, flatulence, burning sensation of tongue, development of duodenal ulcer.

Haematologic: leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis.

Nervous system/Psychiatric: ataxia, numbness, increased hand tremor, muscle twitching, blepharospasm, trismus, activation of latent Horner's syndrome, euphoria, and dementia, depression with suicidal tendencies and Dopamine Dysregulation Syndrome.

Description of selected adverse reactions

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder seen in some patients treated with carbidopa/ levodopa. Affected patients show a compulsive pattern of dopaminergic drug misuse above doses adequate to control motor symptoms, which may in some cases result in severe dyskinesias (see also section 4.4).

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments containing levodopa including Sinemet CR (see section 4.4. 'Special warnings and precautions for use')

Skin: increased sweating.

Special senses: diplopia, dilated pupils, oculogyric crises.

Urogenital: urinary retention, urinary incontinence, priapism.

Miscellaneous: weight gain, oedema, weakness, faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, malignant melanoma (see 4.3 Contraindications), Henoch-Schonlein purpura.

Convulsions have occurred; however, a causal relationship with levodopa or levodopa/carbidopa combinations has not been established.

Reporting of suspected adverse reactions

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

4.9 Overdose

Management of acute overdosage with 'Sinemet CR' or 'Half Sinemet CR' is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of 'Sinemet CR' or 'Half Sinemet CR'.

Electrocardiographic monitoring should be instituted and the patient observed carefully for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as 'Sinemet CR' or 'Half Sinemet CR' should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

5. Pharmacological properties

5.1 Pharmacodynamic properties

'Sinemet CR' and 'Half Sinemet CR' are a combination of carbidopa, an aromatic amino acid decarboxylase inhibitor, and levodopa, the metabolic precursor of dopamine, in a polymer-based controlled-release tablet formulation, for use in the treatment of Parkinson's disease. 'Sinemet CR' and 'Half Sinemet CR' are particularly useful to reduce 'off' time in patients treated previously with a conventional levodopa/decarboxylase inhibitor combination who have had dyskinesias and motor fluctuations.

Patients with Parkinson's disease treated with preparations containing levodopa may develop motor fluctuations characterised by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations ('on-off' phenomenon) is characterised by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, it has been demonstrated that they can be attenuated by treatment regimens that produce steady plasma levels of levodopa.

Levodopa relieves the symptoms of Parkinson's disease by being decarboxylated to dopamine in the brain. Carbidopa, which does not cross the blood-brain barrier, inhibits only the extracerebral decarboxylation of levodopa, making more levodopa available for transport to the brain and subsequent conversion to dopamine. This normally obviates the necessity for large doses of levodopa at frequent intervals. The lower dosage reduces or may help eliminate gastro-intestinal and cardiovascular side-effects, especially those which are attributed to dopamine being formed in extracerebral tissues.

'Sinemet CR' and 'Half Sinemet CR' are designed to release their active ingredients over a four-six hour period. With this formulation there is less variation in plasma levodopa levels and the peak plasma level is 60% lower than with conventional 'Sinemet', as established in healthy volunteers.

In clinical trials, patients with motor fluctuations experienced reduced 'off'-time with 'Sinemet CR' when compared with 'Sinemet'. The reduction of the 'off'-time is rather small (about 10%) and the incidence of dyskinesias increases slightly after administration of 'Sinemet CR' compared to standard 'Sinemet'. Global ratings of improvement and activities of daily living in the 'on' and 'off' state, as assessed by both patient and physician, were better during therapy with 'Sinemet CR' than with 'Sinemet'. Patients considered 'Sinemet CR' to be more helpful for their clinical fluctuations, and preferred it over 'Sinemet'. In patients without motor fluctuations, 'Sinemet CR' under controlled conditions, provided the same therapeutic benefit with less frequent dosing than with 'Sinemet'. Generally, there was no further improvement of other symptoms of Parkinson's disease.

5.2 Pharmacokinetic properties

The pharmacokinetics of levodopa following administration of 'Sinemet CR' were studied in young and elderly healthy volunteers. The mean time to peak plasma levodopa level after 'Sinemet CR' was approximately two hours compared to 0.75 hours with 'Sinemet'. The mean peak plasma levodopa levels were 60% lower with 'Sinemet CR' than with 'Sinemet'. The *in vivo* absorption of levodopa following administration of 'Sinemet CR' was continuous for 4 to 6 hours. In these studies, as with patients, plasma levodopa concentrations fluctuated in a narrower range than with 'Sinemet'. Because the bioavailability of levodopa from 'Sinemet CR' relative to 'Sinemet' is approximately 70%, the daily dosage of levodopa in the controlled release formulation will usually be higher than with conventional formulations. There was no evidence that 'Sinemet CR' released its ingredients in a rapid or uncontrolled fashion.

The pharmacokinetics of levodopa following administration of 'Half Sinemet CR' were studied in patients with Parkinson's disease. Chronic three month, open-label, twice daily dosing with 'Half Sinemet CR' (range: 50 mg carbidopa, 200 mg levodopa up to 150 mg carbidopa, 600 mg levodopa per day) did not result in accumulation of plasma levodopa. The dose-adjusted bioavailability for one 'Half Sinemet CR' tablet was equivalent to that for one 'Sinemet CR' tablet. The mean peak concentration of levodopa following administration of one 'Half Sinemet CR' tablet was greater than 50% of that following one 'Sinemet CR' tablet. Mean time-to-peak plasma levels may be slightly less for 'Half Sinemet CR' than for 'Sinemet CR'.

It is not known whether or not or to what extent the absorption is influenced by a protein rich diet. The bioavailability may be influenced by drugs which affect the gastro-intestinal propulsion.

5.3 Preclinical safety data

The medicine has appeared harmful in animal trials (visceral and skeletal malformations in rabbits). For reproductive toxicity, see section 4.6 'Pregnancy and lactation'.

6. Pharmaceutical particulars

6.1 List of excipients

Hydroxypropylcellulose

Magnesium Stearate

Poly (Vinyl Acetate-Crotonic Acid) Copolymer

Quinoline Yellow 10 Aluminium Lake E104 (Sinemet CR only)

Red Iron Oxide E172

For use with question 95, 96 + 97, *please turn over*:

Tresiba 100 units/mL, 200 units/mL Pre filled (FlexTouch), 100 units/mL Cartridge (Penfill)

Summary of Product Characteristics Updated 15-May-2017 | Novo Nordisk Limited

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. Name of the medicinal product

Tresiba▼ 100 units/mL solution for injection in pre-filled pen

Tresiba▼ 200 units/mL solution for injection in pre-filled pen

Tresiba▼ 100 units/mL solution for injection in cartridge

2. Qualitative and quantitative composition

Tresiba 100 units/mL solution for injection in pre-filled pen

One pre-filled pen contains 300 units of insulin degludec in 3 mL solution.

1 mL solution contains 100 units insulin degludec* (equivalent to 3.66 mg insulin degludec).

Tresiba 200 units/mL solution for injection in pre-filled pen

One pre-filled pen contains 600 units of insulin degludec in 3 mL solution.

1 mL solution contains 200 units insulin degludec* (equivalent to 7.32 mg insulin degludec).

Tresiba 100 units/mL solution for injection in cartridge

One cartridge contains 300 units of insulin degludec in 3 mL solution.

1 mL solution contains 100 units insulin degludec* (equivalent to 3.66 mg insulin degludec).

*Produced in *Saccharomyces cerevisiae* by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.

Clear, colourless, neutral solution.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year.

4.2 Posology and method of administration

Posology

Tresiba is a basal insulin for once-daily subcutaneous administration at any time of the day, preferably at the same time every day.

The potency of insulin analogues, including insulin degludec, is expressed in units (U). One (1) unit (U) of insulin degludec corresponds to 1 international unit (IU) of human insulin, 1 unit of insulin glargine (100 units/mL), or 1 unit of insulin detemir.

In patients with type 2 diabetes mellitus, Tresiba can be administered alone or in any combination with oral antidiabetic medicinal products, GLP-1 receptor agonists and bolus insulin (see section 5.1).

In type 1 diabetes mellitus, Tresiba must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.

Tresiba is to be dosed in accordance with the individual patient's needs. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose.

As with all insulin products adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Tresiba 100 units/mL and Tresiba 200 units/mL solution for injection in a pre-filled pen

Tresiba is available in two strengths. For both, the needed dose is dialled in units. The dose steps, however, differ between the two strengths of Tresiba.

• With Tresiba 100 units/mL a dose of 1–80 units per injection, in steps of 1 unit, can be administered.

• With Tresiba 200 units/mL a dose of 2–160 units per injection, in steps of 2 units, can be administered. The dose is provided in half the volume of 100 units/mL basal insulin products.

The dose counter shows the number of units regardless of strength and **no** dose conversion should be done when transferring a patient to a new strength.

Flexibility in dosing time

On occasions when administration at the same time of the day is not possible, Tresiba allows for flexibility in the timing of insulin administration (see section 5.1). A minimum of 8 hours between injections should always be ensured. There is no clinical experience with flexibility in dosing time of Tresiba in children and adolescents.

Patients who forget a doseare advised to take it upon discovery and then resume their usual once-daily dosing schedule.

Initiation

Patients with type 2 diabetes mellitus

The recommended daily starting dose is 10 units followed by individual dosage adjustments.

Patients with type 1 diabetes mellitus

Tresiba is to be used once daily with meal-time insulin and requires subsequent individual dosage adjustments.

Transfer from other insulin medicinal products

Close glucose monitoring is recommended during the transfer and in the following weeks. Doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted.

Patients with type 2 diabetes mellitus

For patients with type 2 diabetes taking once-daily basal, basal-bolus, premix or self-mixed insulin therapy, changing the basal insulin to Tresiba can be done unit-to-unit based on the previous basal insulin dose followed by individual dosage adjustments.

A dose reduction of 20% based on the previous basal insulin dose followed by individual dosage adjustments should be considered when

- transferring to Tresiba from twice-daily basal insulin

- transferring to Tresiba from insulin glargine (300 units/mL)

Patients with type 1 diabetes mellitus

For patients with type 1 diabetes a dose reduction of 20% based on the previous basal insulin dose or basal component of a continuous subcutaneous insulin infusion regimen should be considered with subsequent individual dosage adjustments based on the glycaemic response.

Use of Tresiba in combination with GLP-1 receptor agonists in patients with type 2 diabetes mellitus

When adding Tresiba to GLP-1 receptor agonists, the recommended daily starting dose is 10 units followed by individual dosage adjustments.

When adding GLP-1 receptor agonists to Tresiba, it is recommended to reduce the dose of Tresiba by 20% to minimise the risk of hypoglycaemia. Subsequently, dosage should be adjusted individually.

Special populations

Elderly patients (≥65 years old)

Tresiba can be used in elderly patients. Glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).

Renal and hepatic impairment

Tresiba can be used in renal and hepatic impaired patients. Glucose monitoring is to be intensified and the insulin dose adjusted on an individual basis (see section 5.2).

Paediatric population

Tresiba can be used in adolescents and children from the age of 1 year (see section 5.1). When changing basal insulin to Tresiba, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise

the risk of hypoglycaemia (see section 4.4).

Method of administration

Tresiba is for subcutaneous use only.

Tresiba must not be administered intravenously as it may result in severe hypoglycaemia.

Tresiba must not be administered intramuscularly as it may change the absorption.

Tresiba must not be used in insulin infusion pumps.

Tresiba is administered subcutaneously by injection in the thigh, the upper arm or the abdominal wall. Injection sites are always to be rotated within the same region in order to reduce the risk of lipodystrophy.

Tresiba 100 units/mL and Tresiba 200 units/mL solution for injection in a pre-filled pen

Tresiba comes in a pre-filled pen (FlexTouch) designed to be used with NovoFine or NovoTwist injection needles.

– The 100 units/mL pre-filled pen delivers 1–80 units in steps of 1 unit.

– The 200 units/mL pre-filled pen delivers 2–160 units in steps of 2 units.

Tresiba 100 units/mL solution for injection in a cartridge

Tresiba comes in a cartridge (Penfill) designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist injection needles.

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

Hypoglycaemia

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.5, 4.8 and 4.9).

In children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimise the risk of hypoglycaemia.

Patients whose blood glucose control is greatly improved (e.g. by intensified insulin therapy) may experience a change in their usual warning symptoms of hypoglycaemia and must be advised accordingly. Usual warning symptoms may disappear in patients with long-standing diabetes.

Concomitant illness, especially infections and fever, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes in the insulin dose.

As with other basal insulin products, the prolonged effect of Tresiba may delay recovery from hypoglycaemia.

Hyperglycaemia

Administration of rapid-acting insulin is recommended in situations with severe hyperglycaemia.

Inadequate dosing and/or discontinuation of treatment in patients requiring insulin may lead to hyperglycaemia and potentially to diabetic ketoacidosis. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased insulin requirement.

Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. In type 1 diabetes mellitus, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Transfer from other insulin medicinal products

Transferring a patient to another type, brand or manufacturer of insulin must be done under medical supervision and may result in the need for a change in dosage.

Combination of pioglitazone and insulin medicinal products

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac failure. This should be kept in mind if treatment with the combination of pioglitazone and Tresiba is considered. If the combination is used, patients should be observed for signs and

symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Eye disorder

Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Avoidance of medication errors

Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between the two different strengths of Tresiba as well as other insulin products.

Patients must visually verify the dialled units on the dose counter of the pen. Therefore, the requirement for patients to self-inject is that they can read the dose counter on the pen. Patients who are blind or have poor vision must be instructed to always get help/assistance from another person who has good vision and is trained in using the insulin device.

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with glucose metabolism.

The following substances may reduce the insulin requirement

Oral antidiabetic medicinal products, GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides.

The following substances may increase the insulin requirement

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no clinical experience with use of Tresiba in pregnant women.

Animal reproduction studies have not revealed any difference between insulin degludec and human insulin regarding embryotoxicity and teratogenicity.

In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually decrease in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements usually return rapidly to pre-pregnancy values.

Breast-feeding

There is no clinical experience with Tresiba during breast-feeding. In rats, insulin degludec was secreted in milk; the concentration in milk was lower than in plasma.

It is unknown whether insulin degludec is excreted in human milk. No metabolic effects are anticipated in the breast-fed newborn/infant.

Fertility

Animal reproduction studies with insulin degludec have not revealed any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients must be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of

hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia (see section 'Description of selected adverse reactions' below).

Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA System Organ Class. Frequency categories are defined according to 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	Frequency
Immune system disorders	*Rare* - Hypersensitivity
	Rare - Urticaria
Metabolism and nutrition disorders	*Very common* - Hypoglycaemia
Skin and subcutaneous tissue disorders	*Uncommon* - Lipodystrophy
General disorders and administration site conditions	*Common* - Injection site reactions
	Uncommon - Peripheral oedema

Description of selected adverse reactions

Immune system disorders

With insulin preparations, allergic reactions may occur. Immediate-type allergic reactions to either insulin itself or the excipients may potentially be life-threatening.

With Tresiba, hypersensitivity (manifested with swelling of tongue and lips, diarrhoea, nausea, tiredness and itching) and urticaria were reported rarely.

Hypoglycaemia

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Lipodystrophy

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

Injection site reactions

Injection site reactions (including injection site haematoma, pain, haemorrhage, erythema, nodules, swelling, discolouration, pruritus, warmth and injection site mass) occurred in patients treated with Tresiba. These reactions are usually mild and transitory and they normally disappear during continued treatment.

Paediatric population

Tresiba has been administered to children and adolescents up to 18 years of age for the investigation of pharmacokinetic properties (see section 5.2). Safety and efficacy have been demonstrated in a long term trial in children aged 1 to less than 18 years. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population (see section 5.1).

Other special populations

Based on results from clinical trials, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

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:

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

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

A specific overdose for insulin cannot be defined; however, hypoglycaemia may develop over sequential stages if a patient is dosed with more insulin than required:

• Mild hypoglycaemic episodes can be treated by oral administration of glucose or other products containing sugar. It is therefore recommended that the patient always carries glucose-containing products.

• Severe hypoglycaemic episodes, where the patient is not able to treat himself, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, long-acting. ATC code: A10AE06.

Mechanism of action

Insulin degludec binds specifically to the human insulin receptor and results in the same pharmacological effects as human insulin.

The blood glucose-lowering effect of insulin is due to the facilitated uptake of glucose following the binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

Pharmacodynamic effects

Tresiba is a basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which insulin degludec is continuously and slowly absorbed into the circulation leading to a flat and stable glucose-lowering effect of Tresiba (see figure 1). During a period of 24 hours with once-daily treatment, the glucose-lowering effect of Tresiba, in contrast to insulin glargine, was evenly distributed between the first and second 12 hours ($AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,total,SS}$ = 0.5).

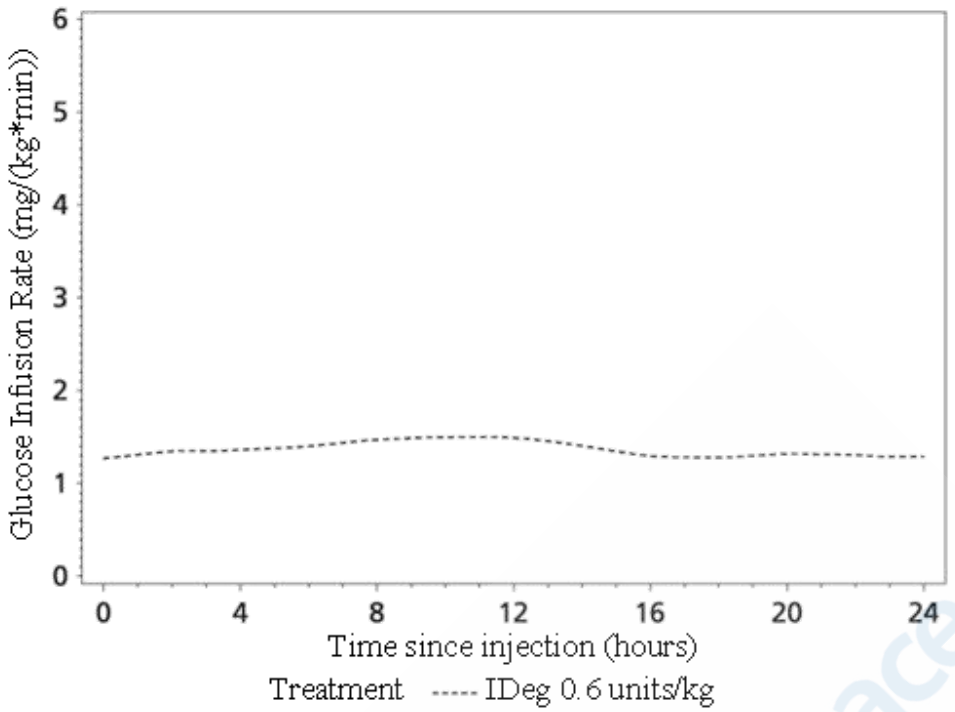


Figure 1 Glucose infusion rate profile, smoothed, steady state - Mean profile 0-24 hours - IDeg 100 units/mL 0.6 units/kg - Trial 1987

The duration of action of Tresiba is beyond 42 hours within the therapeutic dose range.

Steady state will occur after 2–3 days of dose administration.

The insulin degludec glucose-lowering action at steady state shows four times lower day-to-day variability in terms of Coefficients of Variation (CV) for the glucose-lowering effect during 0-24 hours ($AUC_{GIR,\tau,SS}$) and 2–24 hours ($AUC_{GIR2\text{-}24h,SS}$) as compared to insulin glargine, see Table 1.

Table 1 Day-to-day variability within-patients in glucose-lowering effect of Tresiba and insulin glargine (100 units/mL) at steady-state in patients with type 1 diabetes mellitus

	Insulin degludec (N26) (CV%)	Insulin glargine (100 units/mL) (N27) (CV%)
Day-to-day variability in glucose-lowering effect during one dosing interval ($AUC_{GIR,\tau,SS}$)	20	82
Day-to-day variability in glucose-lowering effect from 2-24 hours ($AUC_{GIR2\text{-}24h,SS}$)	22	92

CV: within-patient coefficient of variation in %

SS: Steady State

$AUC_{GIR,2\text{-}24h}$: metabolic effect in last 22 hours of dosing interval (i.e., not influenced by i.v. insulin during the clamp run-in period).

The total glucose-lowering effect of Tresiba increases linearly with increasing doses.

The total glucose-lowering effect is comparable for Tresiba 100 units/mL and 200 units/mL after administration of the same doses of the two products.

There is no clinically relevant difference in the pharmacodynamics of Tresiba between elderly and younger adult patients.

Clinical efficacy and safety

11 multinational clinical trials of 26 or 52 weeks' duration were conducted as controlled, open label, randomised, parallel, treat-to-target trials exposing 4,275 patients to Tresiba (1,102 in type 1 diabetes mellitus and 3,173 in type 2 diabetes mellitus).

In the open-label trials the effect of Tresiba was tested in patients with type 1 diabetes mellitus (Table 3), in insulin naïve patients (insulin initiation in type 2 diabetes mellitus, Table 4) and in previous insulin users (insulin intensification in type 2 diabetes mellitus, Table 5) with fixed as well as flexible dosing time (Table 6), and the reduction in HbA_{1c} from baseline to end of trial was confirmed to be non-inferior in all trials against all comparators (insulin detemir and insulin glargine (100 units/mL)). While improvements in HbA_{1c} were non-inferior compared to other insulin products, against sitagliptin Tresiba was statistically significantly superior in reducing HbA_{1c} (Table 5).

In a prospectively planned meta-analysis across seven open-label treat-to-target confirmatory trials in patients with type 1 and type 2 diabetes mellitus, Tresiba was superior in terms of a lower number of treatment emergent confirmed hypoglycaemic episodes (driven by a benefit in type 2 diabetes mellitus, see Table 2) and nocturnal confirmed hypoglycaemic episodes compared to insulin glargine (100 units/ml) (administered according to label). The reduction in hypoglycaemia was achieved at a lower average FPG level with Tresiba than with insulin glargine.

Table 2 Hypoglycaemia meta-analysis outcomes

	Confirmed hypoglycaemia[a]	
Estimated risk ratio (Insulin degludec/Insulin glargine)	Total	Nocturnal
Type 1 + Type 2 diabetes mellitus (pooled)	0.91*	0.74*
Maintenance period [b]	0.84*	0.68*
Geriatric patients ≥65 years	0.82	0.65*
Type 1 diabetes mellitus	1.10	0.83
Maintenance period [b]	1.02	0.75*
Type 2 diabetes mellitus	0.83*	0.68*
Maintenance period [b]	0.75*	0.62*
Basal only therapy in previously insulin-naïve	0.83*	0.64*

*Statistically significant [a] Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose <3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m. [b] Episodes from week 16.

There is no clinically relevant development of insulin antibodies after long-term treatment with Tresiba.

Table 3 Results from open-label clinical trials in type 1 diabetes mellitus

	52 weeks of treatment		26 weeks of treatment	
	Tresiba[1]	**Insulin glargine (100 units/mL)[1]**	**Tresiba[1]**	**Insulin detemir[1]**
N	**472**	**157**	**302**	**153**
HbA_{1c} (%)				
End of trial	7.3	7.3	7.3	7.3
Mean change	-0.40	-0.39	-0.73	-0.65
	Difference: -0.01 [-0.14; 0.11]		*Difference: -0.09[-0.23; 0.05]*	
FPG (mmol/L)				
End of trial	7.8	8.3	7.3	8.9
Mean change	-1.27	-1.39	-2.60	-0.62
	Difference: -0.33 [-1.03; 0.36]		*Difference: -1.66 [-2.37; -0.95]*	

Rate of hypoglycaemia (per Patient year of exposure)				
Severe	0.21	0.16	0.31	0.39
Confirmed[2]	42.54	40.18	45.83	45.69
	Ratio: 1.07 [0.89; 1.28]		*Ratio: 0.98 [0.80; 1.20]*	
Nocturnal confirmed[2]	4.41	5.86	4.14	5.93
	Ratio: 0.75 [0.59; 0.96]		*Ratio: 0.66 [0.49; 0.88]*	

1 In a once-daily regimen + insulin aspart to cover mealtime insulin requirements

2 Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose <3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 4 Results from open-label clinical trials in insulin naïve type 2 diabetes mellitus (insulin initiation)

	52 weeks of treatment		26 weeks of treatment	
	Tresiba[1]	**Insulin glargine (100 units/mL)[1]**	**Tresiba[1]**	**Insulin glargine (100 units/mL)[1]**
N	**773**	**257**	**228**	**229**
HbA_{1c} (%)				
End of trial	7.1	7.0	7.0	6.9
Mean change	-1.06	-1.19	-1.30	-1.32
	Difference: 0.09 [-0.04; 0.22]		*Difference: 0.04 [-0.11; 0.19]*	
FPG (mmol/L)				
End of trial	5.9	6.4	5.9	6.3
Mean change	-3.76	-3.30	-3.70	-3.38
	Difference: -0.43 [-0.74; -0.13]		*Difference: -0.42 [-0.78; -0.06]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe	0	0.02	0	0
Confirmed[2]	1.52	1.85	1.22	1.42
	Ratio: 0.82 [0.64; 1.04]		*Ratio: 0.86 [0.58; 1.28]*	
Nocturnal confirmed[2]	0.25	0.39	0.18	0.28
	Ratio: 0.64 [0.42; 0.98]		*Ratio: 0.64 [0.30; 1.37]*	

1 Once-daily regimen + metformin ± DPP-IV inhibitor

2 Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose <3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 5 Results from open-label clinical trials in type 2 diabetes mellitus: left – prior basal insulin users, right – insulin naïve

	52 weeks of treatment		26 weeks of treatment	
	Tresiba[1]	**Insulin glargine**	**Tresiba[2]**	**Sitagliptin[2]**

		(100 units/mL)[1]		
N	**744**	**248**	**225**	**222**
HbA_{1c} (%)				
End of trial	7.1	7.1	7.2	7.7
Mean change	-1.17	-1.29	-1.56	-1.22
	Difference: 0.08 [-0.05; 0.21]		*Difference: -0.43 [-0.61; -0.24]*	
FPG (mmol/L)				
End of trial	6.8	7.1	6.2	8.5
Mean change	-2.44	-2.14	-3.22	-1.39
	Difference: -0.29 [-0.65; 0.06]		*Difference: -2.17 [-2.59; -1.74]*	
Rate of hypoglycaemia (per patient year of exposure)				
Severe hypoglycaemia	0.06	0.05	0.01	0
Confirmed[3]	11.09	13.63	3.07	1.26
	Ratio: 0.82 [0.69; 0.99]		*Ratio: 3.81 [2.40; 6.05]*	
Nocturnal confirmed[3]	1.39	1.84	0.52	0.30
	Ratio: 0.75 [0.58; 0.99]		*Ratio: 1.93 [0.90; 4.10]*	

1 Once-daily regimen + insulin aspart to cover mealtime insulin requirements ± metformin ± pioglitazone

2 Once-daily regimen ± metformin SU/glinide ± pioglitazone

3 Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose <3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

Table 6 Results from an open-label clinical trial with flexible dosing of Tresiba in type 2 diabetes mellitus

	26 weeks of treatment		
	Tresiba[1]	**Tresiba Flex[2]**	**Insulin glargine (100 units/mL)[3]**
N	**228**	**229**	**230**
HbA_{1c} (%)			
End of trial	7.3	7.2	7.1
Mean change	-1.07	-1.28	-1.26
	Difference: -0.13 [-0.29; 0.03][5]	*Difference: 0.04 [-0.12; 0.20]*	
FPG (mmol/L)			
End of trial	5.8	5.8	6.2
Mean change from baseline	-2.91	-3.15	-2.78
	Difference: -0.05 [-0.45; 0.35][5]	*Difference: -0.42 [-0.82; -0.02]*	
Rate of hypoglycaemia (per patient year of exposure)			

Severe	0.02	0.02	0.02
Confirmed[4]	3.63	3.64	3.48
	Ratio: 1.10 [0.79; 1.52][6]	*Ratio: 1.03 [0.75; 1.40]*	
Nocturnal confirmed[4]	0.56	0.63	0.75
	Ratio: 1.18 [0.66; 2.12][6]	*Ratio: 0.77 [0.44; 1.35]*	

1 Once-daily regimen (with main evening meal) + one or two of the following oral antidiabetes agents: SU, metformin or DPP-4 inhibitor

2 Flexible once-daily regimen (intervals of approximately 8–40 hours between doses) + one or two of the following oral antidiabetes agents SU, metformin or DPP-4 inhibitor

3 Once-daily regimen + one or two of the following oral antidiabetes agents: SU, metformin or DPP-4 inhibitor

4 Confirmed hypoglycaemia was defined as episodes confirmed by plasma glucose <3.1 mmol/L or by the patient needing third party assistance. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m.

5 The difference is for Tresiba Flex – Tresiba

6 The ratio is for Tresiba Flex/Tresiba.

In a 104-week clinical trial, 57% of patients with type 2 diabetes treated with Tresiba (insulin degludec) in combination with metformin achieved a target HbA_{1c} <7.0%, and the remaining patients continued in a 26-week open label trial and were randomised to add liraglutide or a single dose of insulin aspart (with the largest meal). In the insulin degludec + liraglutide arm, the insulin dose was reduced by 20% in order to minimise the risk of hypoglycaemia. Addition of liraglutide resulted in a statistically significantly greater reduction of HbA_{1c} (-0.73% for liraglutide vs -0.40% for comparator, estimated means) and body weight (-3.03 vs 0.72 kg, estimated means). The rate of hypoglycaemic episodes (per patient year of exposure) was statistically significantly lower when adding liraglutide compared to adding a single dose of insulin aspart (1.0 vs 8.15; ratio: 0.13; 95% CI: 0.08 to 0.21).

Furthermore, two 64-week controlled, double-blind, randomised, cross-over, treat-to-target trials were conducted in patients with at least one risk factor for hypoglycaemia and with type 1 diabetes mellitus (501 patients) or type 2 diabetes mellitus (721 patients). Patients were randomised to either Tresiba or insulin glargine (100 units/mL) followed by cross-over. The trials evaluated the rate of hypoglycaemia upon treatment with Tresiba compared to insulin glargine (100 units/mL) (see Table 7).

Table 7 Results from the double-blind, cross-over clinical trials in type 1 and type 2 diabetes mellitus

	Type 1 diabetes mellitus		**Type 2 diabetes mellitus**	
	Tresiba[1]	**Insulin glargine (100 units/mL)[1]**	**Tresiba[2]**	**Insulin glargine (100 units/mL)[2]**
N	**501**		**721**	
HbA_{1c} (%)				
Baseline	7.6		7.6	
End of treatment	6.9	6.9	7.1	7.0
FPG (mmol/L)				
Baseline	9.4		7.6	
End of treatment	7.5	8.4	6.0	6.1
Rate of severe hypoglycaemia[3]				
Maintenance period[4]	0.69	0.92	0.05	0.09
	Ratio: 0.65 [0.48; 0.89]		*Ratio: 0.54 [0.21; 1.42]*	

Rate of severe or BG confirmed symptomatic hypoglycaemia[3,5]				
Maintenance period[4]	22.01	24.63	1.86	2.65
	Ratio: 0.89 [0.85; 0.94]		*Ratio: 0.70 [0.61; 0.80]*	
Rate of severe or BG confirmed symptomatic nocturnal hypoglycaemia[3,5]				
Maintenance period[4]	2.77	4.29	0.55	0.94
	Ratio: 0.64 [0.56; 0.73]		*Ratio: 0.58 [0.46; 0.74]*	

1 In a once-daily regimen + insulin aspart to cover mealtime insulin requirements

2 In a once-daily regimen ± OADs (any combination of metformin, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor, thiazolidinediones, and sodium glucose cotransporter-2 inhibitor)

3 Per patient year of exposure

4 Episodes from week 16 in each treatment period

5 Blood glucose (BG) confirmed symptomatic hypoglycaemia was defined as episodes confirmed by a plasma glucose value of less than 3.1 mmol/L, with symptoms consistent with hypoglycaemia. Nocturnal confirmed hypoglycaemia was defined as episodes between midnight and 6 a.m

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of trials with Tresiba in:

• Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and children from birth to less than 10 years of age with type 2 diabetes mellitus on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset (see section 4.2 for information on paediatric use).

The efficacy and safety of Tresiba have been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). Patients in the Tresiba arm included 43 children aged 1–5 years, 70 children aged 6–11 years and 61 adolescents aged 12–17 years. Tresiba dosed once daily showed similar reduction in HbA_{1c} at week 52 and greater reduction in FPG from baseline versus the comparator insulin detemir dosed once or twice daily. This was achieved with 30% lower daily doses of Tresiba compared to insulin detemir. The rates (events per patient-year of exposure) of severe hypoglycaemia (ISPAD definition; 0.51 vs 0.33), confirmed hypoglycaemia (57.71 vs 54.05) and nocturnal confirmed hypoglycaemia (6.03 vs 7.60) were comparable with Tresiba versus insulin detemir. In both treatment arms, children aged 6-11 years had a numerically higher rate of confirmed hypoglycaemia than in the other age groups. A numerically higher rate of severe hypoglycaemia in children aged 6-11 years in the Tresiba arm was observed. The rate of hyperglycaemic episodes with ketosis was significantly lower for Tresiba versus insulin detemir, 0.68 and 1.09, respectively. No safety issues were identified with Tresiba with respect to adverse events and standard safety parameters. Antibody development was sparse and had no clinical impact. Efficacy and safety data for adolescent patients with type 2 diabetes mellitus have been extrapolated from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Tresiba in adolescent patients with type 2 diabetes mellitus.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, soluble and stable multi-hexamers are formed creating a depot of insulin in the subcutaneous tissue. Insulin degludec monomers gradually separate from the multi-hexamers thus resulting in a slow and continuous delivery of insulin degludec into the circulation.

Steady state serum concentration is reached after 2–3 days of daily Tresiba administration.

During a period of 24 hours with once-daily treatment, the exposure of insulin degludec was evenly distributed between the first and second 12 hours. The ratio between $AUC_{GIR,0\text{-}12h,SS}$ and $AUC_{GIR,\tau,SS}$ was 0.5.

Distribution

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma.

Biotransformation

Degradation of insulin degludec is similar to that of human insulin; all metabolites formed are inactive.

Elimination

The half-life after subcutaneous administration of Tresiba is determined by the rate of absorption from the subcutaneous tissue. The half-life of Tresiba is approximately 25 hours independent of dose.

Linearity

Dose proportionality in total exposure is observed after subcutaneous administration within the therapeutic dose range. In direct comparison, requirements for bioequivalence are met for Tresiba 100 units/mL and Tresiba 200 units/mL (based on $AUC_{IDeg,\tau,SS}$ and $C_{max,IDeg,SS}$).

Gender

There is no gender difference in the pharmacokinetic properties of Tresiba.

Elderly patients, race, renal and hepatic impairment

There is no difference in the pharmacokinetics of insulin degludec between elderly and younger adult patients, between races or between healthy subjects and patients with renal or hepatic impairment.

Paediatric population

Pharmacokinetic properties of insulin degludec in children (1–11 years) and adolescents (12–18 years) were at steady state comparable to those observed in adults with type 1 diabetes mellitus. Total exposure after a single dose was, however, higher in children and adolescents than in adults with type 1 diabetes mellitus.

5.3 Preclinical safety data

Non-clinical data reveal no safety concerns for humans based on studies of safety pharmacology, repeated dose toxicity, carcinogenic potential, and toxicity to reproduction.

The ratio of mitogenic relative to metabolic potency for insulin degludec is comparable to that of human insulin.

6. Pharmaceutical particulars

6.1 List of excipients

Glycerol

Metacresol

Phenol

Zinc acetate

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Substances added to Tresiba may cause degradation of insulin degludec.

Tresiba must not be added to infusion fluids.

This medicinal product must not be mixed with any other product.

6.3 Shelf life

30 months.

Tresiba 100 units/mL solution for injection in pre-filled pen

After first opening, the product may be stored for a maximum of 8 weeks. Do not store above 30°C. Can be stored in a refrigerator (2°C – 8°C).

Tresiba 200 units/mL solution for injection in pre-filled pen

After first opening, the product may be stored for a maximum of 8 weeks. Do not store above 30°C. Can be stored in a refrigerator (2°C – 8°C).

Tresiba 100 units/mL solution for injection in cartridge

After first opening, the product may be stored for a maximum of 8 weeks. Do not store above 30°C. Do not refrigerate.

For use with question 109:

Pharmacy stamp *Please don't stamp over age box*	Age D.O.B	Title, Forename, Surname & Address Mr J St John's Road NW11 1NZ
Number of day's treatment		NHS Number
Endorsements	Lithium Carbonate 250mg film coated tablet Take one tablet twice daily Mitte: 56 Amitriptyline 10mg Take one in the evening, then increase to two tablets in the evening after 3 days, then three tablets in the evening after 3 days mdu Mitte: 28	
Signature of Prescriber		Date 15/12/2020
For Dispenser No. Of Prescns. on form	Dr Amazing 1234567 The Best Surgery 700 Lovely Street, WC1 1JN FP10	

For use with question 110:

Pharmacy stamp *Please don't stamp over age box*	Age D.O.B	Title, Forename, Surname & Address Mr K 219 York Avenue UB5 5SD
Number of day's treatment		NHS Number

Endorsements	Zomorph 60mg modified-release capsules CD Twice a day Sixty (60) capsules Mirtazapine 45mg tablets One daily 28 tablets Levothyroxine 50microgram tablets One daily 28 tablets
Signature of Prescriber	Date 15/12/2020
For Dispenser No. Of Prescns. on form	Dr Amazing 1234567 The Best Surgery 700 Lovely Street, WC1 1JN FP10

For use with question 111:

Pharmacy stamp *Please don't stamp over age box*	Age D.O.B	Title, Forename, Surname & Address Mrs L Help Me Avenue NW10 7LQ
Number of day's treatment		NHS Number
Endorsements	Vancomycin 1g powder 1g PO every 12 hours Mitte: 14	
Signature of Prescriber *JR*	Date 15/12/2020	
For Dispenser No. Of Prescns. on form	Dr Amazing 1234567 The Best Surgery 700 Lovely Street, WC1 1JN FP10	

For use with question 119 + 120:

Wound management products and elasticated garments

The table below gives suggestions for choices of primary dressing depending on the type of wound (a secondary dressing may be needed in some cases).

PINK (epitheliasing)

Low exudate	Moderate exudate
• Low adherence dressing • Vapour-permeable films and membranes • Soft polymer dressings • Hydrocolloid dressings	• Soft polymer dressings • Foam dressings • Alginate dressings

RED (granulating)

Symptoms or signs of infection, see **Wounds with signs of infection**

Low exudate	Moderate exudate	Heavy exudate
• Low adherence dressing • Soft polymer dressings • Hydrocolloid dressings • Foam dressings	• Hydrocolloid dressings • Foam dressings • Alginate dressings	• Hydrocolloid dressings • Alginate dressings • Foam dressings

YELLOW (Sloughy)(granulating)

Symptoms or signs of infection, see **Wounds with signs of infection**

Low exudate	Moderate exudate	Heavy exudate
• Hydrocolloid dressings • Hydrogel dressings	• Hydrocolloid dressings • Alginate dressings	• Alginate dressings • Capillary-acting dressings • Hydrocolloid-fibrous dressings

BLACK (Necrotic/ Eschar)

Symptoms or signs of infection, see **Wounds with signs of infection**

Low exudate	Moderate exudate	Heavy exudate
• Hydrocolloid dressings • Hydrogel dressings	• Hydrocolloid dressings • Foam dressings • Hydrocolloid-fibrous dressings	

Wounds with signs of infection

Consider systemic antibacterials if appropriate; also consider odour-absorbent dressings

For malodourous wounds with slough or necrotic tissue, consider mechanical or autolytic debridement

Low exudate	Moderate exudate	Heavy exudate
• Honey dressings • Low adherence dressing • Iodine dressings • Hydrocolloid dressings	• Hydrocolloid dressings • Foam dressings • Alginate dressings • Honey dressings • Iodine dressings	• Hydrocolloid dressings • Foam dressings • Alginate dressings • Alginate dressings