

# Cytisine

# Cytisine

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## Summary

This briefing summarises what we know about the effectiveness and safety of tablets containing cytisine as a smoking cessation aid.

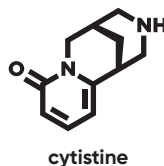
**Cytisine is a safe and effective treatment.** It works in a similar way to varenicline (Champix), reducing urges to smoke by attaching to some of the same neuronal receptors in the brain that nicotine does. Its side effects (gastric symptoms and sleep disturbance) are like those found with varenicline, but less common.

Cytisine is swallowed as a tablet or capsule. **The standard course of treatment is currently 25 days.** Using it for up to 12 weeks is probably more effective and it appears to be roughly as effective as varenicline when taken for the same duration (12 weeks). Even with 25 days' dosing, evidence suggests that it is as effective as nicotine replacement therapy (nicotine transdermal patch, gum, lozenge, nasal spray, inhalator and mouth spray).

Cytisine is available in many countries throughout the world, including Canada and Poland where it can be bought over the counter. It has been **used in parts of Europe for several decades as an effective smoking cessation aid with no apparent serious side effects.**

**Cytisine is now available in the UK as a prescription-only medication.**

The term cytisine is both the generic name and the brand (proprietary) name of the product sold in the UK. In this briefing we use an upper-case C for the brand name (Cytisine) and a lower-case c for the generic name (cytisine). Cytisine has different brand names in different countries (e.g. Tabex, Desmoxan).



## Background

### Existing pharmacological treatments to aid smoking cessation

In the UK several pharmacological treatments to aid smoking cessation are, or have been, widely used:

- nicotine replacement therapy (NRT)
- bupropion (Zyban)
- varenicline (Chantix)
- nicotine vapes (e-cigarettes)

These all significantly increase the chances of long-term success at stopping smoking.

**NRT** (nicotine transdermal patch, gum, lozenge, nasal spray, inhalator and mouth spray) is safe and raises the likelihood of achieving long-term abstinence.<sup>1,2</sup> Use of the nicotine transdermal patch plus a faster-acting product such as gum, lozenge or inhalator (combination NRT) is more effective than using a single product alone. The main side effects that can occur are irritation at the site of use, nausea and sleep disturbance. These NRT products are available on prescription and to buy directly from pharmacies and other kinds of retail outlet. They are used in approximately 15% of quit attempts in the UK.<sup>3</sup>

**Bupropion (Zyban)** is licensed for use in the US (under the brand name Wellbutrin) as an anti-depressant as well as a smoking cessation aid. It has similar effectiveness to NRT. It carries a slight risk of causing a seizure and of an allergic reaction.<sup>2</sup> A common side effect is insomnia. It is not to be used by people with a history of epilepsy, those with eating disorders or alcohol dependence, under 18s or women who are pregnant or breastfeeding. It is available only on prescription and is used in fewer than 1% of quit attempts in the UK.<sup>3</sup>

**Varenicline (Champix)** is more effective than NRT or bupropion.<sup>2,4</sup>

It received a marketing licence in the UK in 2007 and became widely used. There were concerns about the possibility that varenicline might increase the risk of serious neuropsychiatric and cardiac events but this is now considered very unlikely given the findings of a large safety randomised trial and several population-level studies.<sup>5</sup> It is not to be used by under 18s or by women who are pregnant or breastfeeding. It was withdrawn in 2020 in the UK over concerns about traces of carcinogens found in batches of the drug. It is out of patent and Pfizer, the company that developed it, has not reintroduced it.

**Nicotine vapes** are generally more effective than NRT in aiding smoking cessation with similar effectiveness to varenicline in clinical trials.<sup>6</sup>

Concerns have been expressed about harms resulting from use but the available evidence supports the view that, while not completely safe, they are considerably safer than smoking cigarettes.<sup>7</sup> They are currently available on general sale and are the most popular stop smoking aid in the UK, being used in approximately 35% of quit attempts.<sup>3</sup> People who use them to stop smoking tend to continue to use them for months or years afterwards.

## History of cytisine

Cytisine was developed by two inspired Bulgarian pharmacologists, Professor Dymitar Paskov and Dr Hristo Dobrev, at the beginning of the 1950s but was not widely used.<sup>8</sup> Under the brand name Tabex, cytisine has been available as a smoking cessation medication in many countries in Central and Eastern Europe since the 1970s.<sup>9</sup> However, widespread use of cytisine only began during the late 1990s in Poland thanks to research by Professor Zatoński and his team, and in collaboration with Professor West and other British scientists.<sup>10,11,12</sup> Cytisine is available in several countries including Poland and Canada without prescription. Poland remains the only country with multiple companies producing affordable over-the-counter cytisine medicine, with sales approaching one million packages per year,<sup>13,14</sup> which contribute to cytisine being a key element of tobacco control globally.<sup>15,16</sup> Until recently cytisine was not licensed for sale in the UK.

## Cytisine overview

**Cytisine is an alkaloid that can be extracted from parts of many plant species, most notably Laburnum seeds.**<sup>17</sup> There are now several formulations of cytisine available in a range of countries, including much of Europe, New Zealand and Canada.

**Cytisine acts as a selective partial agonist on the alpha-4 beta-2 nicotinic acetylcholine receptor, which plays an important role in nicotine dependence.**<sup>17</sup> In that respect its mode of action is very similar to varenicline. As a partial agonist it causes a limited amount of activation of neural pathways involving that receptor (enough to control urges to smoke) and blocks the receptor so that nicotine (e.g. from smoking a cigarette) cannot attach itself to it.

A formulation similar to Tabex and called simply Cytisine **has received marketing approval by the Medicines and Healthcare Regulatory Authority (MHRA)**; this is the only formulation currently to have a marketing licence in the UK. The licence is held by Bonteque Consulting Ltd in the UK on behalf of Aflofarm in Poland. Distribution of this medication by Consilient Health, whose UK office is based in London, began in early **2024**.

Evidence suggests that 12 weeks of treatment is likely to be more effective than the prescribed 25 days of treatment.<sup>4</sup> **Consideration could be given to dosing for longer than 25 days and up to 12 weeks although this is outside the terms of the MHRA marketing approval** and the appropriate dosing for the extended period has not been determined.

**We would advise that patients access the form of cytisine approved by the MHRA and prescribed by a GP rather than online versions whose provenance and authenticity are not certain.** Reviews on online marketplaces cast doubt on the quality of some products, and the lack of instructions in English is also an issue. The first two examples given below should be avoided; the third offers the future possibility of a dosing schedule that is easier for users to manage.

1. Tabex is the original brand of cytisine, manufactured in Bulgaria, and consists of tablets containing 1.5mg which are taken orally. Starting with six tablets per day five days before stopping smoking, dosage reduces gradually to two tablets per day over 25 days. It is identical to the licensed version but it **does not** have marketing approval in the UK. Nonetheless, it is advertised on several retail websites, including Amazon, costing around £15 for a 25-day course.
2. Desmoxan is the brand name given to cytisine capsules manufactured in Poland by Aflofarm who manufacture the licensed form of cytisine in the UK. Desmoxan has an identical formulation to the UK Cytisine brand. It consists of capsules containing 1.5mg to be taken under the same dosing schedule as Tabex. It **does not** have a marketing licence in the UK but is advertised on several retail websites, costing around £20–30 for a 25-day course.
3. Cytisinicline is also a name given to the chemical cytisine, and was coined by Achieve Life Sciences, a US pharmaceutical company that is testing formulations and dosing regimens in clinical trials. It could become available in the UK within the next few years.<sup>18</sup> The likely formulation will involve a higher dose per tablet but fewer tablets per day.



## Efficacy and effectiveness

**Cochrane Systematic Review found that cytisine significantly improved quit rates.**<sup>19</sup>

In 2011 a large randomised trial, carried out to modern standards, was published confirming previous findings that **cytisine was a safe and effective treatment to aid smoking cessation.**<sup>12</sup> Since then, several other trials have confirmed the safety and effectiveness of the approved 25-day cytisine reducing dose schedule.

One open label trial in New Zealand found it to be more effective than NRT.<sup>15</sup> Other stop smoking medications such as NRT, varenicline and bupropion, are typically licensed for 8–12 weeks or more, whereas cytisine treatment is licensed for 25 days, which makes direct comparison difficult. However, a trial in New Zealand found that 12 weeks of **cytisine had similar effectiveness to varenicline,**<sup>20</sup> while a trial in Australia found that 25 days (3.5 weeks) of cytisine dosing was probably less effective than 12 weeks (84 days) of varenicline.<sup>21</sup> A very large placebo-controlled trial of cytisine in tuberculosis patients in Bangladesh and Pakistan did not show clear evidence of benefit.<sup>22</sup>

Reviews of evidence from randomised controlled trials, including the trial in Bangladesh and Pakistan, estimated that on average **cytisine increased smoking cessation rates compared with a placebo by approximately 75%.**<sup>17</sup>

There have been no modern randomised trials of cytisine undertaken without any behavioural support and so its effectiveness in that context is unknown. The same is true of varenicline, nicotine vapes and bupropion. With NRT there have been some trials purportedly without behavioural support but by their nature randomised trials require a certain amount of involvement with clinical staff.

Observational data from England have shown that quit attempts involving the use of varenicline provided by prescription have higher success rates than quit attempts not using pharmacotherapy.<sup>23</sup> Quit attempts using NRT bought over the counter do not have higher success rates than those using no pharmacotherapy. Evidence on whether people that smoke in the general population who use nicotine vapes in quit attempts have higher success rates than those who try to quit without any pharmacotherapy is mixed.<sup>24</sup>

The head-to-head comparisons between cytisine and varenicline found **side effects to be less common for cytisine.**<sup>20,21</sup> Cytisine's main known side effects are gastric symptoms and sleep disturbance.<sup>17</sup>

## Instructions for use

Each tablet contains **1.5mg of cytisine**. One pack of Cytisine contains 100 tablets which is a complete treatment course (25 days).

Cytisine should be taken with water according to the following schedule with **the quit date no later than the fifth day of treatment**:

Days of treatment	Recommended dosing	Maximum daily dose
From the 1st to the 3rd day	1 tablet every 2 hours	6 tablets
From the 4th to the 12th day	1 tablet every 2.5 hours	5 tablets
From the 13th to the 16th day	1 tablet every 3 hours	4 tablets
From the 17th to the 20th day	1 tablet every 5 hours	3 tablets
From the 21st to the 25th day	1–2 tablets a day	2 tablets

Below is an easier to follow version of the schedule which can also be found in the NCSCT document *Cytisine summary and dosing guidance*:

[www.ncsct.co.uk/publications/Cytisine-SPC](http://www.ncsct.co.uk/publications/Cytisine-SPC)

Days of treatment	1st to 3rd			4th to 12th								13th to 16th				17th to 20th				21st to 25th				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Recommended dosing	1 tablet every 2 hours			1 tablet every 2.5 hours								1 tablet every 3 hours				1 tablet every 5 hours				1–2 tablets a day				
Maximum daily dose	6 tablets			5 tablets								4 tablets				3 tablets				2 tablets				

**If patients use more Cytisine than the recommended dose they might suffer from symptoms similar to nicotine overdose.** Based on data from people who have ingested large quantities of cytisine in a suicide attempt, the symptoms of cytisine overdose include malaise (general feeling of discomfort), nausea, vomiting, tachycardia (increased heart rate), fluctuations in blood pressure, breathing problems, blurred vision and convulsions. If patients develop any of these symptoms, they should **stop taking Cytisine and contact their doctor or pharmacist.**

**If patients forget to use Cytisine** they should **not** take a double dose to make up for the forgotten dose. They should just take their next dose as indicated.



## Safety, contraindications and side effects

Cytisine is licensed for smoking cessation and reduction of nicotine cravings in those who are willing to stop smoking.

The treatment goal of Cytisine is the permanent cessation of the use of nicotine-containing products.

The use of Cytisine allows for a gradual reduction of nicotine dependence by relieving craving and withdrawal symptoms.

In one form or another cytisine has been used in Europe by several million people who smoke, mostly without prescription, and to date there has been no evidence of any serious adverse events. Nevertheless, it is also wise to be cautious when prescribing medicines.

The following contraindications and cautions are from the original licence for cytisine when it was made available in Europe in the 1970s. They have been imported directly into the UK licence without modification. To modify them would require a lengthy and expensive process, and possibly additional clinical trials with specific patient groups.

A lack of clinical experience or safety data means that Cytisine is **not recommended** for patients:

- with **renal** (kidney) **impairment**
- with **hepatic** (liver) **impairment**
- **over 65 years of age**
- **under 18 years of age**

The general safety profile of cytisine is likely to be similar to that of varenicline, but with fewer side effects.

## Contraindications

According to the Summary of Product Characteristics, Cytisine should **not be used** if patients have:

- hypersensitivity to cytisine
- hypersensitivity to any of the excipients (non-active ingredients): mannitol, microcrystalline cellulose, magnesium stearate, glycerol dibehenate and hypromellose
- unstable angina (chest pain caused by reduced blood supply to the heart)
- had recent myocardial infarction (heart attack)
- clinically significant arrhythmias (irregular or abnormal heart rhythm)
- had a recent stroke

or are

- pregnant or breastfeeding

Women of childbearing age using hormonal contraception should **add a secondary barrier method whilst taking cytisine** as its impact on the effectiveness of oral contraceptives is not known.

## Cautions

According to the Summary of Product Characteristics, Cytisine should be taken **with caution** if patients have:

- ischemic heart disease
- heart failure
- hypertension (high blood pressure)
- pheochromocytoma (tumor in the adrenal glands)
- atherosclerosis (thickening or hardening of the arteries) and other peripheral vascular diseases
- gastric and duodenal ulcer
- gastroesophageal reflux disease
- hyperthyroidism (overactive thyroid)
- diabetes
- schizophrenia

This does not mean that Cytisine should not be used. The caution should be discussed with the client, risks assessed and a close eye kept on any possible worsening of these conditions if Cytisine is used.<sup>25</sup>

## Drug interactions

Cytisine should **not be used with anti-tuberculosis drugs**.

According to the approved product information for Cytisine, clients are advised **not to combine it with nicotine-containing products** and health professionals always have to be cautious when prescribing a medicine in a way that is 'off label'. However, our understanding of the pharmacology of cytisine and nicotine, and the fact that the label allows for smoking and cytisine dosing during the first few days of treatment, suggests that it is safe. There may be situations such as hospital in-patient stays where patients could be started on NRT and cytisine from the first day of treatment. It should be stressed, however, that we do not have direct evidence of the safety and efficacy of this approach.

In some cases, as a result of stopping smoking, with or without Cytisine, an adjustment of the dose of other medicines may be necessary. This is especially important for medicines which contain theophylline (to treat asthma), clozapine (for schizophrenia) and ropinirole (to treat Parkinson's disease). See here for information on monitoring and dose changes when individuals taking certain medicines stop, start or re-start smoking: [www.sps.nhs.uk/articles/managing-specific-interactions-with-smoking](http://www.sps.nhs.uk/articles/managing-specific-interactions-with-smoking)

## Side effects

**Like all medicines, Cytisine can cause side effects, although not everybody will experience them.**

Clinical studies and experience indicate **good tolerability of Cytisine**. The proportion of patients in research studies who discontinued treatment because of adverse reactions was 6–15.5% and in controlled studies it was comparable to the proportion in the placebo group.

**Cytisine has no influence on the ability to drive and use machines.**



Mild to moderate side effects are the most likely to occur, and most frequently concern the gastrointestinal tract.

**Most adverse reactions occur when Cytisine is started, and they usually resolve during treatment.** Some of these symptoms could also be the result of smoking cessation, rather than the use of Cytisine.

The following information on side effects by frequency is from the Summary of Product Characteristics. These are symptoms that were observed in early trials of cytisine and were not necessarily more prevalent than in those receiving placebo or no treatment. In some cases (e.g. irritability, weight gain, change in appetite) they are likely to be the symptoms of nicotine withdrawal associated with stopping smoking.

### Side effects by frequency

**Very common** (may affect **more than 1 user in 10**): change in appetite (mainly increase), weight gain, dizziness, irritability, mood changes, anxiety, hypertension, dry mouth, diarrhoea, rash, fatigue, sleep disorders (insomnia, drowsiness, lethargy, abnormal dreams, nightmares), headaches, tachycardia, nausea, alters some flavours, heartburn, constipation, vomiting, abdominal pain (especially in the upper abdomen), muscle pain.

**Common** (may affect **1 to 10 users in 100**): difficulty in concentration, slow heart rate, abdominal distension, burning tongue, malaise.

**Uncommon** (affects **1 to 10 users in 1,000**): feeling of heaviness in the head, decreased libido, lacrimation (abnormal or excessive secretion of tears), dyspnea (shortness of breath), increased sputum (phlegm), excessive salivation, sweating, decreased elasticity of the skin, tiredness, increase in serum transaminase levels.

Side effects listed by system organ class can be found in Annex 1.

## Overdose

Symptoms that may be observed with an overdose of cytisine include:

- malaise
- nausea
- vomiting
- tachycardia
- blood pressure fluctuations
- breathing disorders
- visual disturbances
- clonic convulsions (seizures)

In all cases of overdose, action should be taken as in acute poisoning: gastric lavage (stomach wash) should be performed, and diuresis (production of extra urine) should be controlled with infusion fluids and diuretics. Anti-epileptic drugs may be used if necessary. Breathing, blood pressure and heart rate should be monitored.

## Reporting of suspected adverse reactions

Reporting of suspected side effects allows for continued monitoring of the risks and benefits of Cytisine. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card scheme:

[www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

## Health and social care professionals: recommendations for practice

Stopping smoking is the most important health behaviour change that people who smoke can make. **The most successful way of stopping smoking is to use a combination of behavioural support and a stop smoking medicine or nicotine substitute.**

Varenicline is an effective treatment but is not readily available. The supply of Zyban has been recommenced but it has a somewhat worse side-effect profile than other stop smoking aids. This leaves a gap in the treatment options for clients who do not want to use NRT, or nicotine vapes. **Cytisine is a safe and effective product** that can fill this gap.

**Practitioners can recommend Cytisine as a treatment medication with confidence**, provided they follow the manufacturer's instructions.

Cytisine is **not** recommended at this stage to people under 18, over 65 or for pregnant or breastfeeding women. Neither is it recommended for people with unstable angina, a recent myocardial infarction, clinically significant arrhythmias or who have had a recent stroke.

There are several **conditions for which Cytisine should be used with caution** (see page 15). Here's what the British National Formulary says about Cautions:

"The information under Cautions can be used to assess the risks of using a drug in a patient who has co-morbidities that are also included in the Cautions for that drug – if a safer alternative cannot be found, the drug may be prescribed while monitoring the patient for adverse effects or deterioration in the co-morbidity."<sup>25</sup>

So, what this means is that in the absence of clinical experience it might be best to use other stop smoking aids with the patient groups listed. If Cytisine is used patients should be **closely monitored for side effects to make sure that it is not making their condition worse.**

**Incorporating Cytisine into the Standard Treatment Programme for delivering behavioural support will maximise patients' chances of quitting successfully:**

[www.ncsct.co.uk/publication\\_ncsct-standard-treatment-programme.php](http://www.ncsct.co.uk/publication_ncsct-standard-treatment-programme.php)

Primary care colleagues should be notified that Cytisine is now included in the treatment options for patients who smoke.

Outcomes should be recorded carefully, to assess effectiveness at both a local and national level. Cytisine is included as a treatment option by NHS Digital and can be recorded in stop smoking services' quarterly returns.

Adverse effects should be reported via the MHRA Yellow Card scheme.

Several possible clinical issues are looked at in the next section.

Further questions are welcomed by the NCSCT [enquiries@ncsct.co.uk](mailto:enquiries@ncsct.co.uk)

## Clinical issues

**Q1. I've heard that varenicline should not be used by people with psychiatric problems. Is the same true for Cytisine?**

*Cytisine is not contra-indicated for people with psychiatric problems and neither is varenicline.*

**Q2. Is it OK to buy Cytisine on the internet?**

*It is often unwise to buy medicine on the internet because of concerns over quality control, the lack of clinical supervision, inadequate patient information leaflets and the risk of being scammed. Health professionals should not recommend that patients do this, but it is ultimately the patient's choice.*

**Q3. When will Cytisine become available to prescribe?**

*Supplies of Cytisine will be available in the UK in early 2024.*

**Q4. Can people use Cytisine and NRT together?**

*This is probably best avoided though there have been studies of NRT and varenicline together which did not show evidence of serious adverse reactions. However, in theory, nicotine from NRT or nicotine vapes may lead to adverse reactions if they are used at the same time as Cytisine (see page 16).*

**Q5. Laburnum seeds are poisonous so is Cytisine really safe?**

*Like many medicines, Cytisine is poisonous in high doses but safe at the doses used in the stop smoking medicines.*

**Q6. Does the quit date have to be on day 5 of the dosing schedule or can it be later?**

*Yes, as quitting on later dates has not been fully researched, so follow the instructions: "Smoking should be stopped no later than on the 5th day of treatment". This allows for an earlier quit date if desired, but a standardised approach will help us be clearer on how well Cytisine works in practice.*

**Q7. What should patients do if they experience adverse side effects?**

*If patients are worried about side effects, it is best to consult with their doctor but if they are mild and tolerable there is no reason to stop taking the medicine. Most side effects get better or even disappear over time. Patients should be reminded that stopping smoking in itself causes a range of withdrawal symptoms and some of what they are experiencing will be among those. Also, the short-term discomfort will lead to long-term gains. Adverse events that give cause for concern should be reported to the MHRA via the Yellow Card scheme.*

**Q8. What should patients do if they smoke after the quit date?**

*Ideally, they should continue with the quit attempt and keep taking the medicine. Having a cigarette after the quit date is not a reason for stopping Cytisine and starting smoking. Given the similarity between cytisine and varenicline it is likely that Cytisine will similarly help clients to resume abstinence after they have lapsed.*

**Q9. The drug label lists several contraindications that seem a bit odd. How strictly should these be adhered to?**

*The contraindications were developed several decades ago, and the reasons that they exist are not always clear. As a rule, it is generally best to stick to the medication recommendations.*

**Q10. Why can't Cytisine be used in patients who are over 65 years of age?**

*All of the cytisine safety studies that informed the Summary of Product Characteristics were carried out on people under 65 years of age and data from more recent studies have not been taken into consideration. Although it is **highly unlikely that there will be any unwanted effects of Cytisine because of age alone**, the lack of safety data means that Cytisine is not licensed for this patient group.*

**Q11. Why are women of childbearing age using oral contraceptives (aka the pill) advised to also use a second, barrier contraceptive method (e.g. condoms) when using Cytisine?**

*It is simply not known whether Cytisine affects the effectiveness of oral contraceptives and so, as an extra precaution, additional contraceptives are recommended.*

**Q12. Why can pregnant women and those breastfeeding who want to give up smoking not use Cytisine?**

*There have been no studies done on the effects of Cytisine on pregnant women, nor on the unborn child or infants who are breastfeeding: because of this lack of safety data Cytisine isn't recommended for this patient group.*

## Conclusion

People who smoke often search for something new, something that they haven't tried before – something that might mean that this time, finally, there might be a fix for their smoking. Cytisine holds this promise. It is not a magic wand, and it won't suit everyone, but as we work towards the goal of a Smokefree 2030, it is a new and important tool in our toolbox.

Cytisine is a safe, effective and cost-effective treatment to aid smoking cessation. It has a mode of action similar to varenicline. It has been used as a smoking cessation aid for several decades in many European countries. It is available over the counter in several countries, and it is now licensed in the UK.

Please let us know about how your clients get on with using Cytisine at [enquiries@ncsct.co.uk](mailto:enquiries@ncsct.co.uk). The NCSCT will update this briefing and its online training and assessment programme as we learn more from you about your experience of using Cytisine as a stop smoking aid.



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## Annex 1

### Side effects by system organ class

#### Metabolism and nutrition disorders

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Very common: change in appetite (mainly increase), weight gain

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#### Nervous system disorders

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Very common: dizziness, irritability, mood changes, anxiety,  
sleep disorders, headaches

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Common: difficulty in concentration

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Uncommon: feeling of heaviness in the head, decreased libido

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#### Eye disorders

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Uncommon: lacrimation

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#### Cardiac disorders

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Very common: tachycardia

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Common: slow heart rate

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#### Vascular disorders

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Very common: hypertension

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#### Respiratory, thoracic, and mediastinal disorders

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Uncommon: dyspnoea, increased sputum

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**Gastrointestinal disorders**

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Very common: dry mouth, diarrhoea, nausea, alters some flavours, heartburn, constipation, vomiting, abdominal pain (especially in the upper abdomen)

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Common: abdominal distension, burning tongue

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Uncommon: excessive salivation

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**Skin and subcutaneous tissue disorders**

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Very common: rash

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Uncommon: sweating, decreased elasticity of the skin

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**Musculoskeletal and connective tissue disorders**

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Very common: myalgia (muscle aches and pains)

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**General disorders and administration site conditions**

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Very common: fatigue

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Common: malaise

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Uncommon: tiredness

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**Investigations**

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Uncommon: increase in serum transaminase levels

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