# 7. QUESTION 7

*Consider the need for proposals for regimen for up titration at the start of therapy as well as down titration at the end of therapy.*

## Response

## 7.1. Is there a need for up-titration when starting therapy?

There are no studies that have been specifically designed to investigate the need for up-titrating paroxetine when starting therapy by investigating the relationship between adverse experiences and starting dose, and there is no experience of comparing up-titration regimens at the start of treatment in the same study. However information relevant to this question can be obtained from placebo-controlled studies conducted with paroxetine in the treatment of Generalised Anxiety Disorder (GAD). In the studies conducted in North America (Studies 641 and 642), the patients initiated paroxetine treatment at 10 mg/day for the first week of treatment and increased the dose to 20 mg/day for the second week of treatment. In the European study (protocol 637), the patients initiated treatment at 20 mg and were maintained at this dosage level for two weeks before any further increases were allowed by protocol. A comparison of the nature and incidence of adverse experiences during the initial two weeks of treatment for patients who initiated at 10 mg/day to those who started treatment at 20 mg/day shows that there are fewer AEs in patients in the 20 mg regimen compared to the 10 mg regimen (Table 7.1). However, caution is necessary for this interpretation because the different starting doses were not employed in the same trial. In addition, cultural differences in how individual adverse events are reported is a factor. The nature of adverse experiences reported in European study 637 was similar to the type reported in the North American studies, 641 and 642, but the frequency of the events was lower for both the placebo and paroxetine groups. Thus, even though the attributable risk for a given event to occur was comparable across the studies, quantitative comparisons using only the active doses would be biased.

**Table 7.1 Incidence of Treatment Phase Emergent Common Adverse Experiences (Reported by 5% or More of Paroxetine Patients - Combined Studies) in the First Two Weeks of Treatment by Preferred Term**
**GAD Studies 637, 641 and 642**

| | Study 637 (20 mg/day start) | | Study 641 (combined groups)** (10 mg/day start) | | Study 642 (10 mg/day start) | |
|---|---|---|---|---|---|---|
| Preferred Term | **Paroxetine** N=187 n (%) | **Placebo** N=185 n (%) | **Paroxetine** N=386 n (%) | **Placebo** N=180 n (%) | **Paroxetine** N=162 n (%) | **Placebo** N=164 n (%) |
| Abnormal Ejaculation* | 1 (2.1) | 0 | 17 (4.4) | 1 (1.3) | 11 (6.8) | 2 (3.6) |
| Asthenia | 10 (5.3) | 2 (1.1) | 38 (9.8) | 5 (2.8) | 21 (13.0) | 4 (2.4) |
| Constipation | 6 (3.2) | 0 | 21 (5.4) | 5 (2.8) | 11 (6.8) | 2 (1.2) |
| Decreased appetite | 4 (2.1) | 0 | 21 (5.4) | 1 (0.6) | 5 (3.1) | 2 (1.2) |
| Diarrhea | 5 (2.7) | 7 (3.8) | 27 (7.0) | 7 (3.9) | 10 (6.2) | 5 (3.0) |
| Dizziness | 5 (2.7) | 1 (0.5) | 23 (6.0) | 6 (3.3) | 1 (0.6) | 6 (3.7) |
| Dry mouth | 4 (2.1) | 2 (1.1) | 50 (13.0) | 6 (3.3) | 11 (6.8) | 4 (2.4) |
| Headache | 9 (4.8) | 5 (2.7) | 62 (16.1) | 24 (13.3) | 10 (6.2) | 11 (6.7) |
| Infection | 2 (1.1) | 0 | 6 (1.6) | 3 (1.7) | 6 (3.7) | 2 (1.2) |
| Insomnia | 4 (2.1) | 1 (0.5) | 27 (7.0) | 11 (6.1) | 7 (4.3) | 8 (4.9) |
| Libido decreased | 3 (1.6) | 0 | 26 (6.7) | 2 (1.1) | 9 (5.6) | 1 (0.6) |
| Nausea | 37 (19.8) | 1 (0.5) | 57 (14.8) | 6 (3.3) | 27 (16.7) | 5 (3.0) |
| Respiratory Disorder | 2 (1.1) | 2 (1.1) | 13 (3.4) | 1 (0.6) | 7 (4.3) | 4 (2.4) |
| Somnolence | 9 (4.8) | 0 | 54 (14.0) | 10 (5.6) | 19 (11.7) | 8 (4.9) |
| Sweating | 0 (0.0) | 2 (1.1) | 10 (2.6) | 2 (1.0) | 8 (4.9) | 3 (1.8) |

*Percentage corrected for gender
**Combining experience from the 20 mg and 40 mg paroxetine groups

On the other hand, using the withdrawal rates for AEs to compare starting regimens may provide for a more robust analysis since it is reasonable to believe that a decision to remove a patient from a trial is based on comparable clinical judgement in Europe and North America. Hence, to assess whether uptitration to the effective dose of 20 mg/day was beneficial, the proportion of patients who withdrew due to adverse experiences during the first two weeks of the study was examined. As can be seen from Table 7.2 below, there is no substantial difference in the proportion of patients withdrawn for AEs in the first two weeks of treatment or for the entire studies whether the starting dose was 10 mg or 20 mg. There were no significant tolerability issues with initiating treatment at 20 mg/day, and no evidence to support the need to titrate patients up to the effective dose of 20 mg.

**Table 7.2 Summary of patients Withdrawing Due to Adverse Experiences from the Studies in the First Two Weeks and Overall GAD Studies 637, 641 and 642**

| | Percentage of Patients Withdrawn Due to AE in the First 2 Weeks | Total Percentage of Patients Withdrawn Due to AE During the Study |
|---|---|---|
| Study 637 | 8.6% | 9.6% |
| Study 642 | 5.6% | 10.5% |
| Study 641 – 20 mg | 7.4% | 10.6% |
| Study 641 – 40 mg | 4.6% | 12.2% |

The above data support the view that it is unnecessary to introduce a delay before reaching an effective dose of paroxetine by uptitrating to 20 mg/day. As demonstrated in the response to Question 1.3, no link has been established between possibly suicide-related events and increasing doses of paroxetine. In addition, and as shown in the response to Question 1.2, paroxetine significantly reduces the risk of possibly suicide-related events in patients at risk of suicidal behaviour. In the sub-group of patients in adult placebo-controlled trials with baseline suicidal ideation , there was a lower incidence of possibly suicide-related events in patients in the paroxetine treated group compared to the placebo group and this difference was statistically significant (paroxetine 15/344 (3.4%), placebo 21/291 (7.2%), odds ratio 0.45, 95% C.I. 0.23, 0.89, p=0.023). Hence, not only does it appear unnecessary to uptitrate to 20 mg/day, such uptitration would introduce unnecessary delay in delivering effective treatment to patients at risk.

This is supported by efficacy measurements in the GAD studies.

Table 7.3 compares the percentage of responders based on CGI global improvement at weeks 1, 2 and endpoint for all three studies. This table shows that there was a higher response rate at week 2 in study 637, in which patients received 20 mg as a starting dose, compared with studies 641 and 642, in which the starting dose was 10 mg. This difference in the response rate is more obvious when the treatment difference versus placebo is examined for each group: in study 637, the treatment difference at week 2 was 13.4% compared with between 2.4% and 4.4 % for studies 641 and 642.

This apparent benefit of starting treatment at 20 mg rather than 10 mg is also supported by the results of other parameters in which a statistically significant effect was consistently seen in study 637 at week 2. For example, in study 637 a statistically significant effect was seen at week 2 for the HAM-A change from baseline (-1.9, OC, p= 0.010) whereas at the same timepoint in the other flexible dose study (642) the treatment difference was only –0.3 (OC, p = 0.576).

**Table 7.3 Proportion of Responders Based on the CGI Global Improvement Score of 1 or 2 for Studies 637, 641 and 642 at Week 1, Week 2 and Endpoint**

| | | Percentage of Responders (CGI Global Improvement) LOCF (trt difference+) | | |
|---|---|---|---|---|
| | Starting dose | Week 1 | Week 2 | Endpoint |
| Study 641- 20 mg | 10 mg | 7.5% (-0.4) | 21.8% (2.4) | 61.7% (16.1*) |
| Study 641 – 40 mg | 10 mg | 9.7% (1.9) | 23.9% (4.4) | 68.0% (22.5*) |
| Study 642 (20-50 mg) | 10 mg | 6.3% (0.7) | 21.1% (3.3) | 62.1% (14.9*) |
| Study 637 (20 –50 mg) | 20 mg | 9.5% (1.3) | 29.3% (13.4*) | 63.0% (13.3*) |

* statistically significant
+ figures in brackets show treatment difference between paroxetine and placebo

## 7.2. Down titration at study end

As with many psychoactive medicines, discontinuation of paroxetine (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances, agitation or anxiety, nausea and sweating. In the majority of patients, these events are mild to moderate and are self-limiting. No particular patient group appears to be at higher risk of these symptoms; it is therefore advised that when paroxetine treatment is no longer required, gradual discontinuation by dose tapering be carried out.

Studies in adults that have included a specified regimen for down-titration of paroxetine dose at the end of treatment have instructed patients to reduce daily dose in steps of 10mg/day per week, and have recommended that paroxetine can be stopped once patients have been stepped down to 20 mg/day and have received that dose for a week. When a down-titration has been specified in paediatric studies, dose was reduced at weekly intervals in steps of 10 mg/day to 10mg/day and patients stopped treatment completely after receiving 10 mg/day for a week.

There have been no comparisons of different down-titration regimens within studies. Hence it cannot be concluded that the above approaches are optimal. There are anecdotal reports of some patients who have required a longer, more gradual approach to down-titration. However, introducing such an approach as routine may introduce prolonged exposure to many patients unnecessarily, and there is no evidence to suggest this as a recommended approach for all. The dose tapering regimen employed in GSK clinical studies of paroxetine, and as reflected in the SPC (Summary of Product Characteristics) provides an experience-based guideline to help prescribers design a schedule for discontinuing paroxetine treatment in their patients. It may not be optimal for all patients, but there are no controlled data that support an alternative regimen.

## 7.3. Conclusions

Observations from the paroxetine GAD development programme in which paroxetine was started at 10 mg/day in two studies and 20 mg/day in a third, suggest that starting at 10 mg/day offers no benefit and delays delivering efficacy.

From clinical studies, there is considerable experience of down titration of paroxetine dose at the end of treatment in steps of 10 mg/day per week, stopping completely once 20 mg/day has been taken for a week. There are no controlled data that support alternative regimens. Suggestions for a more gradual approach to the withdrawal of paroxetine should take into consideration that the majority of patients stopping paroxetine do not report withdrawal events, and in those that do, such events are generally mild or moderate in severity and self-limiting.