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# Ophthalmological Events in Patients Receiving Risedronate

## Summary of Information Gained Through Follow-Up in a Prescription-Event Monitoring Study in England

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## Abstract

**Background:** In the UK, the nitrogen bisphosphonate risedronate is licensed for the prevention and treatment of osteoporosis and corticosteroid-induced osteoporosis in postmenopausal women. It is also licensed for the treatment of Paget's disease. During a prescription-event monitoring (PEM) study on risedronate we noted a number of ophthalmological events. Recently, case reports of ophthalmological adverse drug reactions in patients taking bisphosphonates were published in the medical literature. The aim of this study was to further evaluate the association of ophthalmological events reported in relation to risedronate treatment during a PEM study on the drug.

**Methods:** An observational cohort study (PEM study) was conducted in England between September 2000 and June 2002. General practitioners (GPs) were asked for follow-up information on selected events. Events followed up were classified as either 'probably', 'possibly' or 'unlikely' to be related to risedronate, using a modified WHO classification. If insufficient information was obtained on the follow-up questionnaire, the cases were categorised as 'unassessable'.

**Results:** Of the total PEM study cohort of 13 643 patients, 11 156 (82%) were females and 2398 (18%) were males. We received 359 reports of ophthalmological events in 313 patients during the entire study period. Of these we followed up 178 events in 178 patients. Nineteen events in 19 patients were assessed as possibly or probably related to risedronate. The age range for these patients was 50–92 years and the time to onset ranged from 7 days to 5 months. Dry eye (six reports), sore eye (five reports) and conjunctivitis (three reports) were the most frequently reported ophthalmological events assessed as probably or possibly related to risedronate therapy. GPs also reported several other inflammatory conditions of the eye, amongst them two events each of iritis and episcleritis as well as one of keratitis. However, the information received on follow up of these events was insufficient to make causality assessments.

**Conclusion:** Patients receiving risedronate can present with a variety of signs and symptoms affecting the eye with different degrees of severity. Patients may present after the first month of treatment. Doctors should have an increased awareness of possible ophthalmological adverse drug reactions in patients receiv-

ing this drug, which may affect the eyesight in a population at increased risk of fracture if they fall.

## Background

Risedronate gained marketing authorisation in the UK for the first time in March 2000. At the time of this prescription-event monitoring (PEM) study, risedronate was licensed at a dosage of 5 mg/day for the prevention and treatment of osteoporosis and corticosteroid-induced osteoporosis in postmenopausal women and for the treatment of Paget's disease at a dosage of 30 mg/day for 2 months.[1,2] In February 2003 a new, weekly preparation of 35mg was licensed.[3] Several studies have shown the effectiveness of risedronate for the licensed indications.[4,5]

Risedronate is a nitrogen-containing pyridinyl bisphosphonate.[6,7] It inhibits farnesyl diphosphate synthetase, an enzyme of the cholesterol pathway, and the expression of HMG-CoA reductase.[8,9] The disruption of these enzymatic processes interferes with cell functioning and leads to a loss of function and, finally, apoptosis.[10,11] Bisphosphonates have also been found to interact with the immunological system and activate gamma delta T cells.[12]

In 1993, the first report was published regarding ocular inflammation in association with bisphosphonate use.[13] More reports followed,[14-29] including the first report for risedronate in 2002 by Vinas and colleagues.[30]

The aim of this follow-up study was to further investigate the association of ophthalmological events reported in relation to risedronate treatment during a PEM study on this drug.[31]

## Methods

### Prescription-Event Monitoring (PEM) Study

Between September 2000 and June 2002 we conducted an observational cohort study on patients in England who were being prescribed risedronate by their general practitioner (GP) using the methodology of PEM. The results have been published in a separate paper.[31] PEM methodology has previously been described in more detail.[32]

Patients were identified by information from dispensed National Health Service prescriptions for risedronate issued by their GP (exposure data). The Prescription Pricing Authority supplied these data in confidence to the Drug Safety Research Unit (DSRU). Outcome data were obtained by sending a questionnaire ('green form') to the prescribing GP of each patient, at least 6 months after the initial prescription was issued for the individual patient. The GPs were asked for demographic details, indication for treatment, start and stop dates, reasons for stopping, suspected adverse drug reactions (ADRs), events reported to the Committee on the Safety of Medicines (CSM), causes of death and events occurring during and after treatment. GPs did not receive any payment for filling out the green form. The definition of an 'event' (any new diagnosis, reason for referral to a consultant or admission to hospital, unexpected deterioration [or improvement] in a concurrent illness, suspected drug reaction or complaint considered of sufficient importance to enter into the patient's notes), was given on the green form.

Using the hierarchical DSRU dictionary, which is arranged in system organ classes similar to the Medical Dictionary for Regulatory Activities (MedDRA), each event was coded onto the DSRU database. In the DSRU dictionary, associated 'doctor summary' terms (terminology used by the prescribing physician) are grouped under 'lower-level' event terms; similarly, related 'lower-level' event terms are grouped under a broader term ('higher-level' term). All returned questionnaires were assessed by medically qualified staff in order to identify possible ADRs and monitor events of clinical interest, such as conjunctivitis.

### Follow-Up Study of Ophthalmological Events

All ophthalmological events reported as ADRs on the green form questionnaire, together with those

for which additional information was required to enable a causality assessment to be made, were followed up by sending a further questionnaire to the reporting GP. This questionnaire requested confirmation that the patient was receiving risedronate at the time the event occurred, information on concomitant medication(s), co-morbidities and whether there was any alternative cause for the ophthalmological event. Doctors were offered £10 as reimbursement for completing the follow-up questionnaire.

Medically qualified staff then made a causality assessment of these selected events into four categories of 'probably', 'possibly', 'unlikely' or 'unassessable', using the DSRU guideline, which is a modification of the WHO classification of causality.[33] The assessor took into account the temporal relationship, pharmacological plausibility, clinical and pathological characteristics of the event and the likelihood or exclusion of other possible causes.

We adhered to ethical guidelines prepared by the Council for International Organizations of Medical Sciences in collaboration with the WHO, the Royal College of Physicians of London and the Multi-Centre Research Ethics Committee.[34-36]

## Data Analysis

Summary statistics for response rate, patient demography, events reported as suspected ADRs and reasons for stopping were calculated during the PEM study and for the follow-up study. Additionally, the time to onset for ophthalmological events assessed as possibly or probably related to risedronate was determined.

In the PEM study, for all events (higher-level terms) reported during treatment with risedronate, incidence rates, expressed as incidence densities (IDs) per 1000 patient months of treatment, were calculated by dividing the number of first reports of an event during a specified time period (t) by the number of patients months of treatment in the same period (t) multiplied by 1000 (equation 1).[32]

$$ID_t = \frac{\text{Number of first reports of event during treatment for period (t)}}{\text{Number of patient months of treatment for period (t)}} \times 1000 \quad \text{(Eq. 1)}$$

For each time period, the patient months of treatment were calculated by totaling the days of treatment for all patients for whom the date of stopping treatment with risedronate was known or who were continuing therapy when the green form was returned to the DSRU. This sum was divided by 30 to calculate the number of patients months of treatment for that period of time. Separate incidence densities were calculated for the first month of treatment ($ID_1$) and for the second to sixth month of treatment ($ID_2$). To investigate whether an event rate was increasing or decreasing between the first month and months 2–6, the difference between these two incidence densities was calculated ($ID_1 - ID_2$) with a 99% CI around the point estimate of the difference between these two values. If the confidence interval was positive and did not include the null value, it indicated that the rate of events in the first month of treatment was significantly greater than in months 2–6. This event was considered as a signal associated with starting risedronate therapy.

## Results

### PEM Study

The cohort of the PEM study comprised 13 643 patients, most of whom were postmenopausal women (table I).

In this study, which took place between September 2000 and June 2002, the median period of observation (the time interval between the date of the first prescription for an individual patient and the date the green form questionnaire was returned) was 10.1 months with an interquartile range (IQR) of 9.3–11.1 months.

Overall, we received 359 reports of ophthalmological events in 313 (2.3% of cohort) patients during the study period. Of these, 296 events in 265 (1.9%) patients occurred during treatment. The 31 events reported as a reason for stopping risedronate

**Table I.** Demographic data reported on green form questionnaires during the prescription-event monitoring study (PEM) on risedronate

| Parameter | Value |
|---|---|
| Questionnaires [n. (%)] | |
| sent | 26 247 |
| returned | 15 181 (57.8) |
| complete with clinical information[a] | 13 643 (52.0) |
| Age[b] [years (IQR)] | |
| females | 73 (64–79) |
| males | 70 (58–77) |
| Sex distribution [n. (%)] | |
| females | 11 156 (81.8) |
| males | 2398 (17.6) |
| not specified | 89 (0.7) |

a 1538 (10.1%) forms were classified as void as no clinical information was provided.

b The age was not specified for 5318 (39.0%) patients.

**IQR** = interquartile range.

therapy in 30 (0.2%) patients included seven events (in seven [<0.1%] patients) also reported as suspected ADRs. None of these seven events were reported to the CSM (figure 1).

One of the higher-level ophthalmological event terms 'visual defect', which includes the lower-level terms diplopia, hemianopia, vision deteriorated, vision field defect and visual disturbance, was identified as being associated with starting treatment with risedronate ($ID_1 = 1.12$; $ID_2 = 0.28$; $ID_1\text{-}ID_2 = 0.83$; 99% CI = 0.01, 1.66).

### Follow-Up Study of Ophthalmological Events

Of the 359 reported ophthalmological events that were reported during this PEM study, 178 events were followed up (including the seven reported as suspected ADRs). Nineteen events were assessed as possibly or probably related to risedronate (figure 2).

The minimal risk in our cohort (13 643 patients) of developing an ophthalmological ADR to risedronate, based only on cases assessed as possibly or probably related to risedronate (19 cases), gives an incidence risk of 1.4 per 1000 patients.

Follow up was not initiated for 181 events because information on the green form was sufficient to exclude an association of these events with the use of risedronate.

Of the group of events assessed as possibly or probably related to risedronate, 18 patients were female and one was male. The youngest patient was 50 years and the oldest was 92 years old (median 70 years, IQR 66–78 years). The indication was given in 15 cases. Eleven patients were treated for osteoporosis, three for corticosteroid-induced osteoporosis and one for Paget's disease. In four cases the indication was not specified. Sixteen individuals were prescribed 5mg/day and one patient was treated with 30mg daily (for Paget's disease). For the other two patients the dose prescribed was not specified.

On the green form, 18 of these events were reasons for stopping risedronate but only two were classified as ADRs to risedronate, whereas on the follow-up questionnaire for nine events the GP stated that they thought that the event was related to risedronate (including the two reported on the green form).

Notable is the relatively long time to onset for these ophthalmological events. In the majority of cases, onset occurred after >1 month of treatment, with a median of 42 days (IQR 23–120 days). None of these events were pre-existing conditions and all patients had a positive dechallenge, although the patient with episcleritis had only improved, but symptoms had not completely resolved, at the time of follow up. Those events assessed as probably related to risedronate also had a positive rechallenge. Three patients were reported to have experienced associated symptoms in other system organ classes apart from the ophthalmological system and one had another ophthalmological event (table II). Seven patients had a relevant past medical history (table III).

## Discussion

The aim of this follow-up study was to gain more detailed information on ophthalmological events of concern reported during the PEM observational cohort study on risedronate and to facilitate evaluation

of the causal association of these events with risedronate treatment.

The main findings are that we identified a number of, mostly reversible, ophthalmological ADRs during risedronate treatment that were not mentioned in the data sheets, not identified by the GP as an ADR nor reported to the CSM.

The general strengths and weaknesses of PEM studies have been described previously.[32] The main advantages of PEM are that exposure and outcome data are collected on large cohorts (usually >10 000 patients) under conditions of everyday clinical practice and include a wide variety of patients. Knowing the number of patients exposed, their duration of therapy and the number of events reported enables PEM studies to calculate incidence risk and/or rate for these events, whereas spontaneous reporting schemes usually only provide the number of ADR reports that were received. PEM does not interfere with the doctor's decision to prescribe the study drug, because patients are identified from dispensed prescriptions (after their prescription was issued by the GP). Also, in PEM studies GPs are asked to report all events that have occurred irrespective of whether they consider them to be causally related to the drug. Hence, PEM is capable of identifying adverse events that none of the prescribers suspected were due to the drug, in contrast to spontaneous reporting schemes where the doctor needs to suspect an ADR.

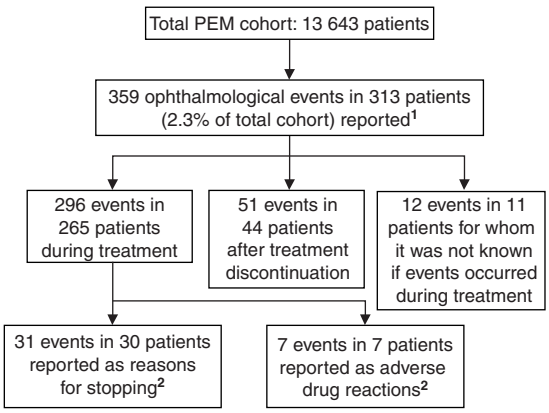


**Fig. 1.** Ophthalmological events reported during the prescription-event monitoring (PEM) study on risedronate. **1** Some patients had more than one ophthalmological event; these events may have occurred during or after stopping risedronate treatment or it was not known if the events occurred during treatment; therefore, the number of patients by treatment category is greater than the total number of patients. **2** An event reported as the reason for stopping risedronate therapy was not necessarily considered by general practitioners to be an adverse drug reaction.

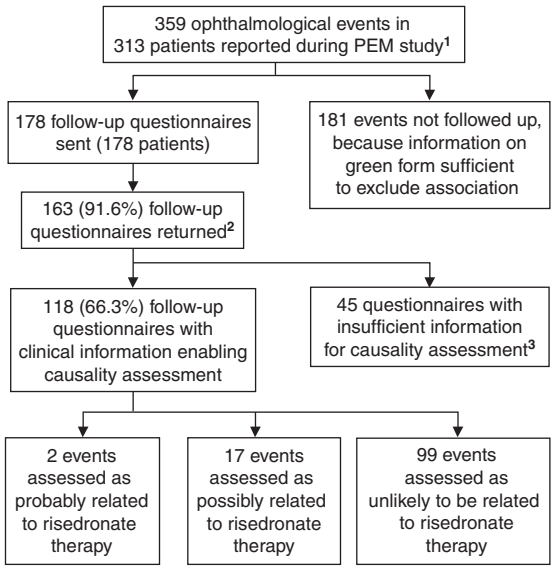


**Fig. 2.** Follow-up study of ophthalmological events identified during the prescription-event monitoring (PEM) study on risedronate. **1** Of these, 296 events were reported during treatment, 51 events were reported after treatment discontinuation and for 12 events it was not known whether they occurred on or off treatment. More detailed information is given in figure 1. **2** Includes one case of subconjunctival haemorrhage reported as an adverse drug reaction (ADR) on the green form. **3** Dry eye (ten events), conjunctivitis (seven events – one of these was reported as an ADR on the green form), cataract (seven events), visual disturbance (six events – two of these were reported as ADRs on the green form), eye pain (two events – one of these was reported as an ADR on the green form), episcleritis (two events), iritis (two events), vision deteriorated (two events) and one event each of keratitis, diplopia, hemianopia, eye irritation, sore eye, vision field defect and floaters (this patient was diagnosed with retinal detachment).

Similar to other pharmacovigilance schemes, PEM is only as good as the information reported and is dependent both on the patient reporting the condition to their GP and the GP recording it on the green form questionnaire. Therefore, it is possible that some serious events may not have been identified and so the risk of ophthalmological events associated with risedronate could be underestimated. As with other observational studies, PEM is not able to verify patient compliance. It may also be affected by

**Table II.** Ophthalmological events assessed as probably or possibly related to risedronate

| Event term | No. of events | Time to onset (days) | Reason for stopping risedronate | Suspected adverse drug reaction by general practitioner on follow-up | Causality assessment by the Drug Safety Research Unit |
|---|---|---|---|---|---|
| Dry eye | 6 | 27, 34, 120, 120, 125, 128 | Yes (5)<br>No[a] (1) | Yes (3)<br>No (1)<br>Don't know (2) | 6 possibly |
| Sore eye[b] | 5 | 23, 28, 42, 46, 150 | Yes (5) | Yes (3)<br>Don't know (2) | 1 probably<br>4 possibly |
| Conjunctivitis | 3 | 14, 29, 100 | Yes (3) | Yes (1)<br>Don't know (2) | 3 possibly |
| Diplopia | 1 | 7 | Yes | Yes | 1 probably |
| Episcleritis | 1 | 94 | Yes | No | 1 possibly |
| Eye irritation | 1 | 7 | Yes | Don't know | 1 possibly |
| Eye pain[c] | 1 | 57 | Yes | Don't know | 1 possibly |
| Visual disturbance[d] | 1 | 9 | Yes | Yes | 1 possibly |
| Total | 19 | Range 7–150 | Yes (18)<br>No (1) | Yes (9)<br>No (2)<br>Don't know (8) | 2 probably<br>17 possibly |

a Risedronate was stopped a month later for an unspecified reason and symptoms did not reoccur.

b For one of the patients muscle cramps were reported at the same time, which resolved on stopping risedronate. Another patient presented with dyspepsia at the same time, which resolved on stopping risedronate.

c This patient also presented with associated photophobia and was seen by an optician, who noted on examination 'tiny blisters on the surface of the conjunctiva'.

d This patient presented with ambylopia, limb pain and headache. Follow-up information was only available on ambylopia (coded to visual disturbance), which resolved upon stopping risedronate.

survivor bias because data are only collected from GPs and, therefore, patients treated only by hospital physicians are not included.

The response rate to our follow-up questionnaires was very good (91.6%) and better than GP surveys.[37,38] It has to be remembered that GPs received a small payment as reimbursement for the work involved filling out the questionnaire. In contrast, there was no payment for filling out the initial green form.

Cases of conjunctivitis, diplopia, episcleritis, eye irritation, eye pain and sore eye were assessed as possibly or probably related to risedronate treatment and these events are not mentioned in the data sheet for either the 30mg or the 5mg preparation. Additionally, dry eye and ambylopia are not mentioned in the product information for the 5mg preparation, but are mentioned in the product information for the 30mg preparation.[1,2] The product information states that "ambylopia, corneal lesion and dry eye occurred with a frequency of 1.6% each in a cohort of 61 patients".

In both data sheets it is mentioned that "iritis was uncommonly reported in clinical trials".[1,2] Although we received two reports of iritis, no causality assessment could be made because of a lack of information. The incidence of ophthalmological events in clinical trials is higher than the incidence risks reported during this PEM study and could be a reflection of the limitations of observational pharmacovigilance studies. In addition there are differences in the monitoring of patients included in clinical trials under well controlled conditions and those treated under 'real life' conditions of general practice that are monitored during PEM studies. Hence, in PEM we are dependent on a third party for reporting events. In addition, the differences in the numbers of patients (n = 61 and 13 643, respectively) should be taken into account if comparing the frequency of an ADR given in the data sheet (1/61 patients) and the number of events identified as an

ADR after causality assessment in a PEM study (19/13 643 patients).

However, it has to be taken into account that the data presented have been made available, in the majority of cases, by GPs and not by ophthalmologists, which may have lead to under-reporting or misreporting of some ophthalmological conditions. In addition, there were 45 events followed up, for which limited follow-up information was received, making assessment of causality not feasible. Therefore, the true rate of ophthalmological ADRs during risedronate treatment may be higher than the one reported here.

Reviewing the current literature it appears that the longer a bisphosphonate has been on the market, the more publications can be found relating to ocular adverse effects. Reporting may also be influenced by the number of patients using a particular bisphosphonate as well as publications about possible adverse effects and alerts created by drug monitoring centres. As risedronate is one of the new generation bisphosphonates, only licensed since 2000 in the UK, it may not be surprising to find only a small number of ocular ADRs reported in the literature. This PEM study was initiated 6 months after market authorisation for the drug and is providing the first large number of case reports with detailed information and causality assessments of ophthalmological events associated with risedronate.

In our study a wide range of symptoms have been reported, with the majority being inflammatory conditions of the eye. As most patients were seen only by their GP, it is difficult to decide whether the described symptoms are all part of one particular inflammatory condition of the eye or are in fact different entities.

Since 1999 six cases of reversible ocular inflammation (four scleritis and two anterior uveitis) have been described in association with the nitrogen bisphosphonate alendronate.[18,21,23,24] In a previous PEM study on alendronate (1995–97), 391 eye events were reported during treatment in a cohort of 11 916 patients. However, no follow-up information to enable causality assessments was obtained.[39]

In 2002 Vinas et al.[30] published the first ocular inflammatory case (episcleritis) associated with the treatment of risedronate. The patient presented on day 7 of treatment with unilateral pain of the eye and redness. A positive dechallenge and rechallenge was reported.

The following year, Fraunfelder and Fraunfelder[15] published a summary of cases collected from spontaneous reporting systems in the US and the WHO, which included seven cases of non-specific conjunctivitis, two of abnormal or blurred vision and one of scleritis associated with risedronate. However, it has to be pointed out that these cases may not all have undergone a 'structured' causality assessment and the quality of the reports may vary,

**Table III.** Relevant past medical history and concomitant medication in patients with events assessed as possibly or probably related to risedronate

| Event | No. of events | Relevant past medical history | Relevant concomitant medication |
|---|---|---|---|
| Dry eye | 6 | Arthritis | None reported |
| | | Crohn's disease | Prednisolone and eye ointment |
| Sore eye | 5 | Polymyalgia rheumatica | None reported |
| Conjunctivitis | 3 | Recurrent subconjunctival haemorrhages | None reported |
| | | Corneal scar and polymyalgia rheumatica | Prednisolone, prednisolone drops |
| | | Coeliac disease | None reported |
| Diplopia | 1 | None reported | Inhaled corticosteroid |
| Episcleritis | 1 | Dry eyes | Eye drops |
| Eye irritation | 1 | None reported | None reported |
| Eye pain | 1 | None reported | None reported |
| Visual disturbance | 1 | None reported | None reported |
| **Total** | **19** | **7** | **4** |

but for all these cases the reporter had a suspicion that the event was related to the use of risedronate. In the same year Health Canada highlighted these concerns by summarising the reports they had received of ocular disorders in association with the use of bisphosphonates. They received three reports of suspected ADRs with two events of blindness and one each of glaucoma, ocular haemorrhage and retinal detachment for risedronate.[40] In 2004, the Australian Adverse Drug Reactions Advisory Committee reported that they had received a small number of reports of ocular disorders associated with the use of bisphosphonates. These included one report associated with risedronate use, although the type of ocular event reported was not specified.[41]

Putting these reports together it appears difficult to find a pattern. This is partly due to the variable quality of information in the reports, an unclear patho-mechanism, the recentness of the problem and the wide variety of clinical symptoms.

The interesting question currently being discussed amongst researchers is whether these observed ocular adverse effects are a class effect of bisphosphonates and what the pathological mechanism for these is. Mbekeani et al.,[18] for example, thought that the nitrogen-containing bisphosphonate alendronate may affect inflammatory mediators. In 2001, Reszka and colleagues[42] published an interesting article about their research on the effects of the nitrogen-bisphosphonates alendronate and risedronate on a cell model for the stratum basale of the oesophagus, which shed more light on the effects of these drugs on cells outside the bone. They showed that both drugs act on enzymatic pathways, which leads to cell growth arrest. If bisphosphonates act on cells of the oesophagus, they might also act on other cells in the body, including the eye. Vinas and colleagues[30] thought these events may be related to the liberation of cytokines and acute phase proteins and cause an immunological reaction, which has been reviewed by Santini et al.[43] The recent discovery that bisphosphonates interfere with the immune system[12] and activate gamma delta T cells is another interesting development and may support the theory by Vinas and his team. This theory may be further strengthened by the finding that dry eye syndrome is related to inflammatory processes mediated through T cells.[44] Existing autoimmune diseases involving the eye (e.g. juvenile rheumatoid arthritis, Reiter's syndrome, sarcoidosis, Behçet's syndrome or ankylosing spondylitis) could serve as models for understanding the pathological mechanism of bisphosphonates in relation to the eye. Maybe there are certain risk groups (i.e. patients with dormant immunological or rheumatological diseases or a certain genetic susceptibility). It is possible that several pathological mechanisms are involved in relation to the observed adverse effects on the eye.

## Conclusion

Risedronate is an important drug for the treatment of osteoporosis and Paget's disease, and only a small number of patients experience ocular events. This follow-up study has contributed to the knowledge about a variety of ophthalmological events observed during risedronate treatment. We identified several events assessed as possibly or probably related to risedronate that are not mentioned in the data sheets.

Prescribing doctors should be aware of these ocular adverse effects and that patients may present with a range of symptoms and considerable delay in time to onset. Recovery may be slow and it is possible that in the future certain risk groups will be identified, for example patients with some pre-existing eye diseases. Until then, increased awareness, consideration of eye events during review of the patient and referral to an ophthalmologist when necessary, as well as stopping the medication, should be considered for all patients taking bisphosphonates. Nevertheless, it is concerning that patients at risk of fractures when falling may experience visual problems through this medication. Further research is needed to try and identify possible risk factors and the pathological mechanism for these ocular adverse effects.

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Conflicts of interest: Professor Saad Shakir has received consultancy and lecturing fees from the manufacturers of products used for the treatment of osteoporosis. Beate Aurich-Barrera, Lynda Wilton and Scott Harris have no conflicts of interest that are directly relevant to this study.

WHO statement: The WHO Collaborating Centre in Uppsala, Sweden states that, with respect to data released from the centre, "the information is not homogenous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction" and that "the information does not represent the opinion of the WHO".

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